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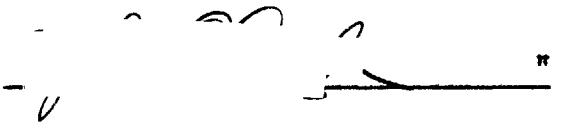

STEREOCHEMICAL ASPECTS OF THE CYCLOHEPTANE RING

A THESIS

Presented to

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by

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STEREOCHEMICAL ASPECTS OF THE CYCLOHEPTANE RING

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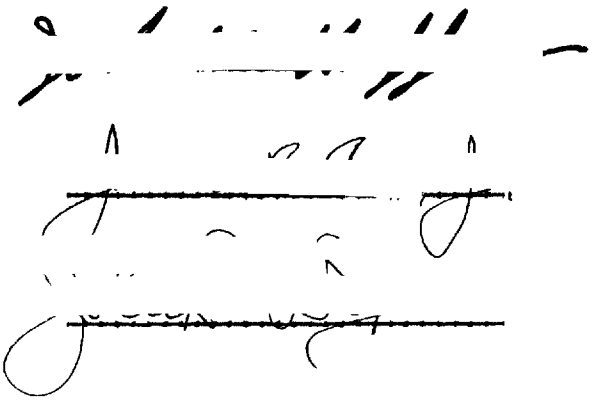

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SUMMARY

It was the purpose of this research to add to the knowledge concerning the stereochemical characteristics of the cycloheptane ring system by a consideration of certain reactions who geometric requirements are well-established. The two reactions chosen were the deamination of the 2-aminocycloheptanols and the dehydration of the 2-phenylcycloheptanols. The former reaction (specifically deaminations conducted with nitrous acid) has been studied carefully in the cyclohexane system using cis- and trans-2-aminocyclohexanol. The present work reports the results of analogous reactions carried out on cis- and trans-2-aminocycloheptanol. The trans aminoalcohol was synthesized by reaction of cycloheptene oxide with aqueous ammonia. This compound was epimerized to the cis aminoalcohol by formation of the p-nitrobenzamide and cyclodehydration to the oxazoline, followed by acid-catalyzed hydrolysis.

The trans-2-aminocyclohexanol upon deamination is reported to yield as the only isolable product cyclopentanecarboxaldehyde, while under the same conditions the cis aminoalcohol produces 70% aldehyde and 30% cyclohexanone. The results are interpreted on the basis of the accepted relative stability of various possible conformations of the cyclohexane system and the established stereochemical requirements for the reaction. Our deaminations of cis- and trans-2-aminocycloheptanol indicate that in the case of the trans alcohol the only product observed in cyclohexanecarboxaldehyde. This is the agreement with the results

in the cyclohexane series. The epimeric cis-2-aminocycloheptanol, however, afforded upon deamination with nitrous acid only ca. 22% of the product resulting from ring contraction, cyclohexanecarboxaldehyde; the remainder was assumed to be cycloheptanone. The deamination mixtures were analyzed by quantitative infrared spectroscopy using the extinctions of the aldehyde and ketone absorption maxima.

The difference in the behavior of cis-2-aminocyclohexanol and cis-2-aminocycloheptanol is explained on the basis of the greater flexibility of cycloheptane systems as opposed to cyclohexane systems. Two products are observed in the case of the cis aminoalcohols because there are two conformations which are of comparable stability, one in which the amino group is equatorial (or quasi-equatorial) and one in which it is axial (or quasi-axial). The former of these conformations leads to the aldehyde by the accepted mechanism of deamination while the latter results in proton loss to afford the ketone. The production of aldehyde and ketone in the ratio of 7:3 corresponds approximately to the relative abundance of the two conformers of cis-2-aminocyclohexanol. This indicates that each of the conformations reacts independently without apparently being affected by the fact that a change to the alternate conformation is possible. The cis-2-aminocycloheptanol molecule on the other hand is apparently flexible enough so that the rate of conformational interchange is more rapid that the sequence of ring contraction affording the aldehyde.

The second part of this study consisted of the dehydration of cis- and trans-2-phenylcycloheptanol. Neither of the required alcohols was a known compound which demanded a careful choice of synthetic route to assure that the stereochemistry of the product would be unequivocal.

The trans alcohol was obtained by the reaction of phenyllithium and cycloheptene oxide. The cis epimer was isolated as the p-nitrobenzoate ester from a reaction mixture resulting from the reduction of 2-phenylcycloheptanone with lithium aluminum hydride.

The lithium aluminum hydride reductions were investigated in some detail because the production of the less stable epimer, as was observed, is unusual. It was found that upon extended contact time the cis alcohol initially formed was apparently epimerized to the more stable trans-2-phenylcycloheptanol. Reduction of 2-phenylcycloheptanone with a "mixed hydride" (lithium aluminum hydride - aluminum chloride) also afforded a preponderance of the trans isomer as would be expected. The analysis of the reduction product mixtures was accomplished by a combination of vapor phase chromatography and infrared spectroscopy.

The two alcohols were dehydrated initially with phosphorus oxychloride in pyridine solution, and the product mixture was analyzed for 1-phenylcycloheptene by quantitative ultraviolet spectroscopy and for total number of components including 1- and 3-phenylcycloheptene by vapor phase chromatography. The trans alcohol produced no measurable amount of conjugated olefin while the cis alcohol yielded 37-39% as determined by the extinction at 247 mμ (λmax., 1-phenylcycloheptene). The vapor phase chromatographic analyses showed that both dehydration mixtures were composed of ca. 50-60% of unknown substances. It was determined that these unidentified products were neither olefinic nor hydroxylic. The possibility of a phosphate ester was also eliminated.

Two additional methods of dehydration were carried out. The first of these made use of thionyl chloride under conditions identical to the

phosphorus oxychloride dehydrations. Organic material was isolable from these reactions only in poor yield, and ultraviolet examination revealed no absorption maximum corresponding to 1-phenylcycloheptene for the product from either the cis and trans alcohol. This method of dehydration was not investigated further. In the second procedure phosphoric acid was employed as a dehydrating agent. This reaction has been studied extensively with regard to cis- and trans-2-phenylcyclohexanol and the olefins formed have been securely established. These studies showed that extensive isomerization takes place in the case of trans-2-phenycycloheptanol. Our study indicates that under similar conditions both cis- and trans-2-phenylcycloheptanol produce a complex mixture of products with the 1- and 3-phenylcycloheptenes constituting only a minor percentage. The unidentified products were not investigated further. It was also shown that 3-phenylcycloheptene is not stable under the reaction conditions which is in direct contrast to the reported stability of 3-phenylcyclohexene. The noted isomerization of the non-conjugated olefin to the conjugated isomer in good yield, of course, invalidates any conclusions which might have been drawn from the measured ratio of 1-phenylcycloheptene to 3-phenylcycloheptene.

The present study of these two reaction types emphasizes the fact that care must be used in generalizing the facts known about cyclohexane systems to include larger rings. In particular the greater flexibility of seven-membered systems must be taken into account as well as the great difference in the number and stability of conformations between cyclohexane and cycloheptane.

I. INTRODUCTION:

STEREOCHEMICAL ASPECTS OF THE CYCLOHEPTANE RING[†]

The development of conformational analysis has led to an ever increasing volume of work on cyclohexane and other systems involving the six-membered ring,[2-4] e.g., the steroids and a large portion of the terpenes. However, the impetus for a similar exhaustive study of larger ring systems has not been present, and much of the stereochemistry of these larger ring systems has been inferred from the considerable data concerning cyclohexane. These analogies are not entirely valid. Certainly, the principles[2-4] invoked to explain the behavior of cyclohexane systems are still operative in larger cyclic molecules, but other factors become important as well. One of these factors which demands consideration is the inherently greater flexibility of larger rings. The increase in ring mobility is notable even in the next higher homolog of cyclohexane, cycloheptane.

To illustrate some of the more striking differences between six- and seven-membered rings, the following facts are considered. It has been found that trans-1,2-cycloheptanedicarboxylic acid readily forms a cyclic anhydride,[††] whereas the formation of trans-1,2-cyclohexanedicarboxylic anhydride is realized only with difficulty. Similarly, both

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[†] This work has been published in part. See ref. 1.

[††] We are indebted to Prof. R. A. Raphael for communicating his results to us prior to their publication. See ref. 5.

cis- and trans-1,2-cycloheptanediols form cyclic ketals with acetone easily,[6,7] whereas, only cis-1,2-cyclohexanediol forms the ketal with facility.[8] The analogous derivative of trans-1,2-cyclohexanediol is made only with difficulty.[9] Both of the 1,2-cycloheptanediols increase the conductivity of boric acid solutions by the formation of cyclic borate esters; neither of the 1,2-cyclohexanediols does so.[6] This evidence all points to the fact that the atoms of a cycloheptane ring are not as rigidly held in one particularly stable arrangement as are the atoms of a cyclohexane ring. To illustrate further the difference between cis and trans isomers of cyclohexane, it has been found that cis-1,2-cyclohexanediol will react with paraformaldehyde to form the simple, cyclic acetal, while under similar conditions the trans diol gives trans-hexahydro-1,3,5-benzotrioxepane.[10]

Some theoretical studies on larger ring systems have been carried out.[11,12] Allinger[11] in comparing the relative stabilities of cyclohexane and cycloheptane conformations concluded that cyclohexane, in the chair form, lies in a very deep and narrow potential energy well, and that the other conformations of cyclohexane are of much higher potential energy. Cycloheptane, on the other hand, cannot achieve nearly so stable a conformation regardless of the fact that seemingly there would be lessened repulsions because of the larger ring. In fact, cycloheptane must either sacrifice optimal valence angles in favor of lessened atomic interaction, or tolerate distorted bond angles in order to reduce the non-bonded interactions of hydrogens which have been forced too close together. In the chair form of cyclohexane the hydrogen atoms on adjacent carbon atoms are as perfectly situated as possible to minimize all

interactions and bond angle strain. The projected angles between any two adjacent substituents is 60°, and, at the same time, the tetrahedral bond angles of the carbon atoms are maintained at nearly 109°. The carbon-carbon bond distances are the optimal 1.54 Ångstroms. The free energy of activation for the chair-chair interconversion of cyclohexane has recently been experimentally estimated as 9.7 kcal./mole.[13] This large value can be attributed to the necessity of altering the favorable situation in the ground state conformation, thereby distorting bond angles and introducing hydrogen-hydrogen non-bonded interactions.

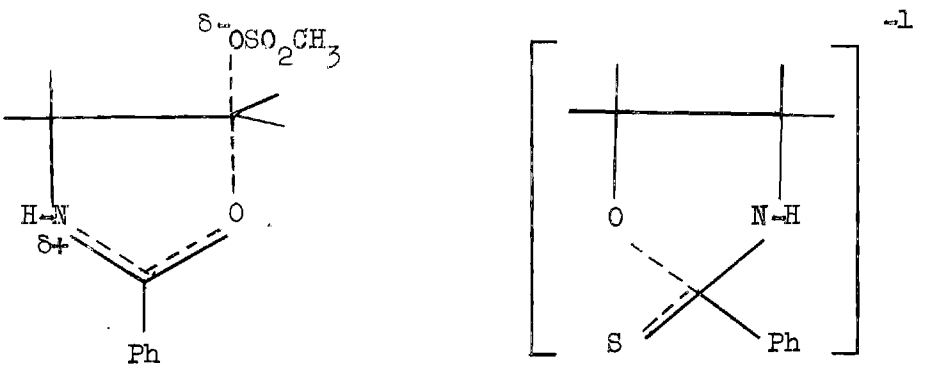
The most favorable conformations available for the cycloheptane ring are not as well defined as those for cyclohexane. However, two general types of conformations related to the boat and chair forms of cyclohexane are the most reasonable. Allinger[11] finds that the calculated enthalpy of the chair form is in agreement with the experimentally determined heat of combustion, but he also states that because of indeterminant quantities in similar calculations on the boat conformation, the proportion of cycloheptane existing in this latter conformation may be appreciable; indeed, it may predominate.

Johnson, et al.,[14] have estimated the enthalpy difference between the boat and chair forms of cyclohexane from the heats of combustion of fused lactone derivatives to be 5.3 ± 0.3 kcal./mole. Calculated values for this same quantity range from 1.31[15] to 10.6 kcal./mole.[16] Pauncz and Ginsberg,[12] by vector analysis, have calculated the energy difference between the boat and chair conformations of cycloheptane using various assumptions and qupte extreme values of 2.75 to 8.13 kcal./mole. One of the factors which adds to the uncertainty of the calculated values for

cycloheptane is the fact that there are considerable hydrogen-hydrogen non-bonded interactions the energetics of which cannot be accurately determined.

Kreevoy, Morgan, and Taylor[17] have recently measured the rates of acid-catalyzed hydrolysis of ketals of some cyclic ketones. Their findings indicate that cycloheptanone diethyl ketal is hydrolyzed at a remarkably faster rate than smaller cyclanone and open-chain ketone derivatives. This is explained in terms of torsional and bond-angle strain in the ground state conformation which is partially relieved in the transition state containing a carbon atom with some trigonal character. The accelerated rate of hydrolysis of the ketal of cycloheptanone indicates on these bases that there is considerable strain in the cycloheptane ring because of eclipsed hydrogens, much more so than in the cyclohexane ring and larger cyclic systems.

Studies along a similar line have been carried out in which the rates of formation of Δ^2-oxazolines by two different routes have been studied. The rates of cyclization of 2-benzamidocycloalkyl methanesulfonates by an anti-parallel mechanism have been measured,[18] as well as the rates of an analogous series of 2-thiobenzamidocyclanols, which react via a syn-parallel mechanism.[19] In the case of the anti-parallel mechanism, the transition state of which is represented by A, it was found that, whereas cis-2-benzamidocycloheptyl methanesulfonate cyclized at a rate comparable to the other compounds studied, the trans isomer reacted about sixty times more rapidly than the next fastest one, trans-2-benzamidocycloeicosanyl methanesulfonate. The rates of cyclization of these very large rings are in agreement with the estimated rates of open-chain



A B

analogs. The second process, the syn-parallel mechanism (structure B represents the transition state) is not nearly so common as the former process. This second study also yields significant results concerning the seven-membered ring. Here, it is not the rate of reaction of the cycloheptane derivatives compared to other members of the series that deserves note, even though cyclization does occur faster than in open-chain compounds, but rather it is the relative rates of the cis- and trans-2-thiobenzamidocycloheptanols which is significant. The value of the ratio, k(trans)/k(cis), is 0.86, comparatively close to unity. Interpretation of this ratio in terms of the energy of the ground state conformation versus the energy of the conformation of the transition state implies that there is approximately the same energy difference between these two states for the epimeric 2-thiobenzamidocycloheptanols. Comparing this fact with the accepted view concerning cyclohexane derivatives, it is seen that there is a significant variation. Conformational studies indicate that the formation of the transition state B from cis-2-thiobenzamidocyclohexanol will alleviate some of the Pitzer strain in

the molecule, while, conversely, the formation of the analogous transition state from the trans isomer will add to the Pitzer strain. An increase in Baeyer or bond angle strain will accompany both processes. It is, therefore, considered that, because of the opposing strain effects in cis cyclohexane derivatives the formation of transition state B occurs with greater facility. Extending this argument to similar cycloheptane compounds it can be inferred from the comparable rates of cyclization of the epimeric 2-thiobenzamidocycloheptanols that the repulsive atomic interactions and bond angle forces act so as to give the same overall result, i.e., the cyclization rate is increased for both isomers to the same order of magnitude. Without attempting to separate these strain effects into individual components it is sufficient to note that these results are in agreement with the facile formation of both cis and trans fused cycloheptano derivatives.

Additional evidence relating to the proximity of substituent groups on the cycloheptane ring stems from recent work on the aminocyclanols themselves. Related to the fact that the pK_a values of dibasic acids are a function of the proximity of the carboxyl groups,[20] is the work of Prelog and Häfliger[21] who demonstrated that the basicity of vicinal aminoalcohols depends on the direct interaction of the two groups through space. In other words, the basicity constant for 2-aminoalcohols is directly related to the geometrical configuration and conformation of the molecule, the amino group becoming more basic as the hydroxyl group approaches. Svoboda, Jonáš, and Sicher[22] have measured the pK_a values of a series of epimeric 2-aminocyclanols and find that from cyclopentane through cycloöctane the cis isomer is the more basic, and that there is

a regular decrease in the difference in the basicity of the two epimers. The trans derivative of cyclononane and higher homologs are the more basic. The fact that the epimeric 2-aminocycloheptanols occur near the minimum difference in basicity indicates that the proximity of the amino and hydroxyl groups in these compounds is more nearly the same than for the corresponding cyclohexane derivatives.

Cope has carried out an extensive study of transannular effects in cyclohexane systems as well as medium-sized and larger rings. His findings include the facts that transannular influence is measurably present in six-membered rings,[23] and that it increases significantly in cycloheptane derivatives,[24] and is very appreciable in cyclooctane systems.[25] This trend indicates a definite increase in the proximity of the opposing ring hydrogens.

It is clear in consideration of the facts presented that simple extensions of the findirgs concerning the cyclohexane system to larger ring systems must be made carefully and with consideration of any peculiarities pertinent to the larger cyclic molecules.

In general, the chemical study of structure by a known reaction mechanism or, conversely, the investigation of a reaction path using compounds of established configuration is influenced by two factors. In flexible molecules the system probably will adapt itself to the steric requirements of the reaction by a change in conformation and, perhaps more subtle, in structures that cannot adapt to the reaction mechanism, the attacking reagent may follow an unexpected, less preferred path. Therefore, one is not able to infer, by determination of the products of a stereospecific reaction on a given compound, the ground state conformation

of that compound. Product determination measurements of this type are directly pertinent only to the conformation of the molecule in the most favorable situation for reaction to occur, or, in a sense, the transition state. In cases where two or more conformations can lead to as many different products, the equilibrium concentrations of the conformers must be considered, as well as the rates of conformational interchange and the kinetic characteristics of each of the conformers toward the attacking reagent. Nonetheless, simple product analysis has proved to be a valuable tool in conformational analysis and, in fact, can yield in addition, qualitative information regarding the relative rates of various stages of the reaction.

The nomenclature developed to describe cyclohexane derivatives is not adequate, as will be seen. In the chair form of cyclohexane there are only two types of carbon-hydrogen bonds. The first of these consists of those which are perpendicular to the average plane of the ring (axial) and the second consists of those which are approximately in the average plane of the ring (equatorial). The more flexible and larger cycloheptane ring allows more possible conformations which results in there being more substituent bond orientations. Thus, the simple designation of axial or equatorial is not sufficient to describe accurately the relative situation of substituents. Nevertheless, in the chair form of cycloheptane one-half of the substituent bonds can be considered approximately equivalent to the equatorial bonds of cyclohexane, although, all of these are not identical in themselves. The other half of the substituent bonds are effectively similar to the axial designation. These bond orientations will, hereafter, be designated respectively, as

"quasi-equatorial" (e') and "quasi-axial" (a').

Our study has centered around two reactions which have been examined carefully in the cyclohexane series, viz., the nitrous acid deamination† of the cis- and trans-2-aminocyclanols[26] and the dehydration of the cis- and trans-2-phenylcyclanols.[28,29] In the cyclohexane series the results of these two reactions have been interpreted with respect to the conformation of the cyclohexane ring system. Implicit in the interpretations were assumptions concerning the mobility or flexibility of cyclohexane. Both of these reactions seemed applicable to analogous cycloheptane derivatives. We have carried out a series of these two reaction types and interpreted the results in the light of the established flexibility of the seven-membered ring, as well as the well-known stereochemical requirements of the reactions.

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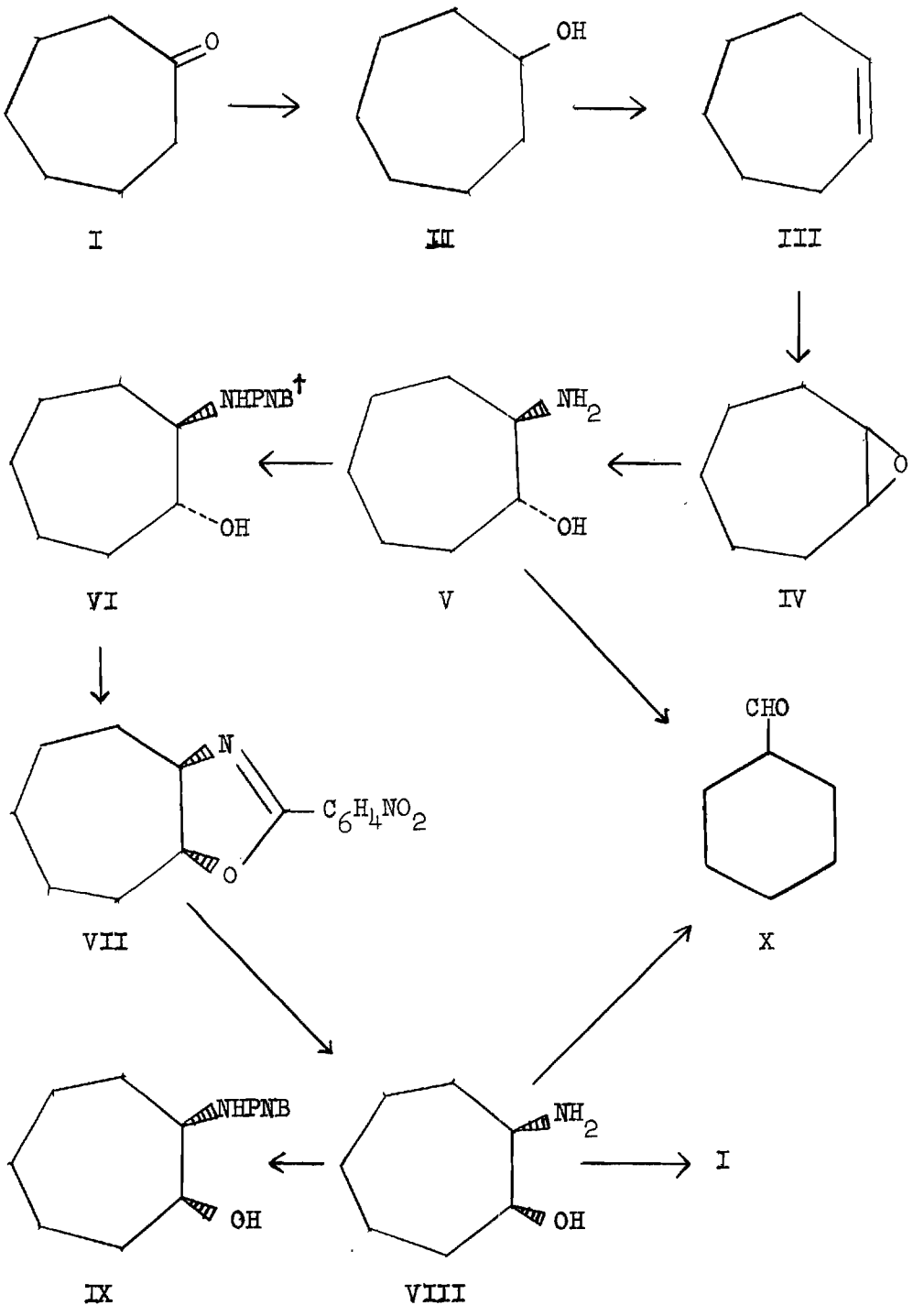
†For early, incomplete deamination studies see ref. 27.

II. DISCUSSION:

DEAMINATION OF *CIS*- AND *TRANS*-2-AMINOCYCLOHEPTANOL

The preparations of *cis*- and *trans*-2-aminocycloheptanol were achieved *via* a well-known, stereospecific route. Cycloheptanone (I) was taken as the initial material; this compound was reduced with sodium borohydride in a cold, aqueous methanol solution to afford cycloheptanol (II). The crude alcohol was then dehydrated to cycloheptene (III) with hot, 85% phosphoric acid. The olefin was oxidized to cycloheptene oxide (IV) with perbenzoic acid. An alternate route to the oxide employing the bromohydrin was also used.[30] In this procedure cycloheptene was converted to *trans*-2-bromocycloheptanol by means of an aqueous slurry of N-bromosuccinimide, and then dehydrohalogenated with cold, 20% sodium hydroxide. The action of aqueous ammonia at elevated temperature on cycloheptene oxide produced *trans*-2-aminocycloheptanol (V) in good yield.[30,31] Distillation and sublimation afforded the pure *trans*-aminoalcohol, m. p. 74 - 75°.

The elegant, general method whereby McCasland converted *trans*-2-aminocyclohexanol[32] to the *cis* isomer seemed to present the most promise for obtaining *cis*-2-aminocycloheptanol (VIII). According to this scheme *trans*-2-aminocycloheptanol was first reacted with *p*-nitrobenzoyl chloride to form *trans*-2-(*p*-nitrobenzamido) cycloheptanol (VI), m. p. 190.5 - 191.5°. This amido alcohol was cyclized to *cis*-2-*p*-nitrophenyl-4,5-cycloheptanooxazoline (VII), m. p. 120 - 121°, by dehydration with thionyl chloride. During the course of the cyclization inversion took place at



†PNB = $-COC_6H_4NO_2$ (para)

the hydroxyl-bearing carbon resulting in a cis fusion of the two rings. Acid hydrolysis cleaved the oxazoline ring system in such a manner so as to leave the configuration of the potential amino- and hydroxyl-bearing carbons unchanged; cis-2-aminocycloheptanol, m. p. 81 - 82°, was prepared in good yield by this route. The cis-aminoalcohol with p-nitrobenzoyl chloride gave cis-2-(p-nitrobenzamido)-cycloheptanol (IX), m. p. 129 - 130°. Sicher and Svoboda[33] recently reported the synthesis of these compounds and found the cis-aminoalcohol to have the m. p. 79 - 81° and the p-nitrobenzamide the m. p. 128 - 129.5°.

The deaminations were carried out by the addition of cold, aqueous sodium nitrite to chilled solutions of the aminoalcohols in aqueous acetic acid. The total chloroform- or ether-soluble fraction was isolated after making the reaction mixture alkaline. The oils resulting from the deaminations were analyzed for carbonyl components by infrared spectroscopy. Deamination of trans-2-aminocycloheptanol afforded as the only identifiable product cyclohexanecarboxaldehyde (X), identical in all respects to a sample prepared from cyclohexylmagnesium bromide and ethyl orthoformate.[34] The infrared spectrum of the crude deamination mixture showed only one absorption maximum in the carbonyl region at 5.81μ.[35] The 2,4-dinitrophenylhydrazone prepared from the total organic fraction crystallized nicely and was easily purified to that of cyclohexanecarboxaldehyde, giving additional evidence of the homogeneity of the product.

Deamination of cis-2-aminocycloheptanol afforded a mixture of cycloheptanone and cyclohexanecarboxaldehyde, the former predominating. Treatment of the crude reaction mixture from the deamination of cis-2-aminocycloheptanol with 2,4-dinitrophenylhydrazine reagent gave

cycloheptanone 2,4-dinitrophenylhydrazone which required several crystallizations to purify. The infrared spectrum of the reaction mixture showed a major carbonyl band at 5.89μ with a shoulder at 5.81μ. Quantitative infrared measurements on two deamination runs indicated that the crude deamination product from cis-2-aminocycloheptanol was 22.5 ± 2.5% aldehyde. The remainder of the product was assumed to be cycloheptanone. Isolation of the total aldehyde fraction from the deamination mixture of the cis-aminoalcohol as the dimedone derivative indicated that 36% of the product was aldehyde. The dimedone derivative isolated from the deamination mixture showed no depression in melting point upon admixture with the same derivative of cyclohexanecarboxaldehyde. The dependence of dimedone derivative formation on several factors including pH prevents this, as carried out, from being an accurate quantitative determination.

The differences observed between the behavior of six- and seven-membered ring systems are striking, especially with regard to these deaminations. cis-2-Aminocyclohexanol gives, predominantly, ring contraction to produce cyclopentanecarboxaldehyde and a lesser amount of proton loss leading to cyclohexanone.[26] The former, as stated, yields for the most part cycloheptanone (Table 1.).

According to the well-known steric requirements for group migration in the nitrous acid deaminations of aminoalcohols,[2-4,36] the amino group must be located antiparallel to the bond which migrates. On this basis, a study of molecular models† of trans-2-aminocycloheptanol indicates that the amino group, and consequently the hydroxyl group, must

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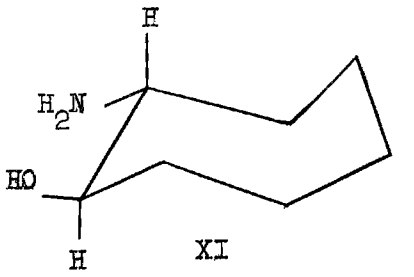
†Barton molecular models were used.

Table 1. Deaminations of cis- and trans-2-Aminoalcohols

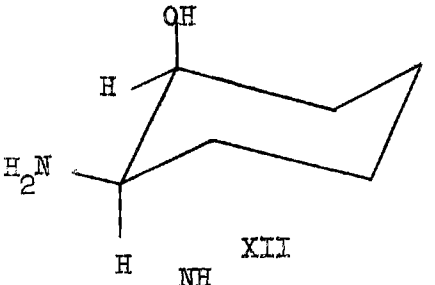
Aminoalcohol	% aldehyde	% ketone
cis-2-aminocyclohexanol[26]	~70	~30
trans-2-aminocyclohexanol[26]	~100	--
cis-2-aminocycloheptanol	~22	~78
trans-2-aminocycloheptanol	~100	--

occupy positions analogous to equatorial positions in cyclohexane compounds, that is, quasi-equatorial (e'). Of the several possible conformations, XI seems to best fulfill these requirements. These results are in accord with those obtained in the cyclohexane series, where trans-2-aminocyclohexanol exclusively gives cyclopentanecarboxaldehyde upon similar treatment with nitrous acid because the carbon-carbon bond is located anti-parallel to the leaving nitrogen in the most stable conformation.

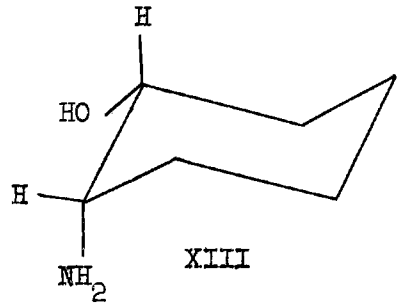
The formation of a large amount of cycloheptanone from the deamination of cis-2-aminocycloheptanol is in direct contrast to the products obtained from the deamination of cis-2-aminocyclohexanol. In the cyclohexane series, deamination of the cis compound proceeds to give about 70% cyclopentanecarboxaldehyde.[26] If it is assumed, as is probable, that the amino group is somewhat larger than the hydroxyl group, then the conformation of cis-2-aminocyclohexanol which would predominate at equilibrium would be that in which the amino group is equatorial and the hydroxyl group is axial (XII). Deamination of a compound of this conformation will proceed with ring contraction to give the aldehyde, whereas, the slightly less favorable conformation (XIII) will give cyclohexanone.



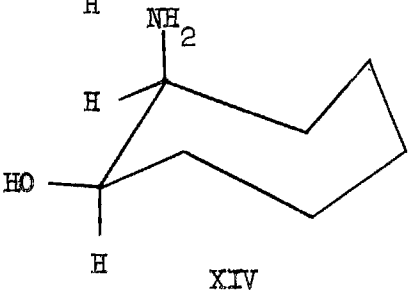
XI



XII



XIII



XIV

The production of cycloheptanone as the principal product in the deamination of cis-2-aminocycloheptanol demands that at the time of reaction the amino group, or a reactive species derived from the amino group, such as a diazonium group, be in a quasi-axial conformation and antiparallel to a hydrogen. These conditions are satisfied by structure XIV. Reaction of cis-2-aminocycloheptanol in conformation XI will lead to ring contraction affording the aldehyde. As we have already seen, as a result of the deamination of cis-2-aminocyclohexanol, the amino group tends to assume an equatorial position in six-membered rings, and as a result of the deamination of trans-2-aminocycloheptanol, bulky groups also occupy a quasi-equatorial position in seven-membered rings. Consequently, we would be led to predict on purely conformational grounds, that the deamination of cis-2-aminocycloheptanol and cis-2-aminocyclohexanol should give very nearly the same ratio of aldehyde to ketone. It is, therefore, difficult to reconcile the large proportion

of cycloheptanone formed from cis-2-aminocycloheptanol in terms of static conformational arguements. These apparently incompatible results can, however, be interpreted in terms of the relatively great flexibility of the cycloheptane ring as compared to that of cyclohexane.

The mechanism of the initial stages of the deamination of aliphatic primary amines should proceed in a manner similar to that of aromatic amines,[37,38] viz., the amine is first converted to an N-nitroso derivative, which can isomerize and dehydrate to an aliphatic diazonium ion. This diazonium ion loses nitrogen forming a carbonium ion, or undergoes nucleophilic attack directly by solvent, reagent, or neighboring group to yield the product of the reaction. Considerable study has been devoted to the actual behavior of these aliphatic diazonium ions and the so-called "hot" carbonium ions[39-42] that are produced by the ejection of molecular nitrogen. The elegant isotopic labelling studies of Collins, et al.,[43,44] on 1,1-diphenyl-2-amino-1-propanol have shown conclusively that the carbonium ions produced by deamination of an amine do have a finite existence. It was demonstrated that such carbonium ions do, in fact, exist long enough for conformational changes to take place, and, in addition, they are present as the open (non-bridged) carbonium ions, in the cases in point, even when a phenyl group is situated conveniently for possible phenonium ion formation. Martin and Bentrude in a recent publication[45] clarify nicely the current evidence on semi-pinacolic rearrangements. In systems somewhat more similar to our work Streitwieser and Cloverdale[46] have shown that in the absence of any groups which could stabilize an intermediate or cause the preference for a particular conformation, the deamination of cis-cyclohexylamine-2-d

proceeds with at least 94% retention of configuration to give cis-cyclohexanol-2-d. This shows that, by whatever mechanism solvolysis occurs the nitrogen cannot have departed completely from the molecule since the carbonium ion so produced would be equally subject to solvolytic attack from either side. This conclusively demonstrates that the loss of nitrogen is not inevitable before some other reaction can take place.

In the case of the cis-2-aminocyclanols the deamination sequence can be described as in Fig. 1.† If it is assumed that the principal conformation of both cis-2-aminocyclohexanol and cis-2-aminocycloheptanol is that in which the amino group is equatorial (or quasi-equatorial) as in structure XV, then the equatorial diazonium ion (XVI) will be that initially formed in the largest amount. This diazonium ion may then follow one of two fruitful reaction paths; it may either undergo decomposition with carbon-carbon bond migration to give ultimately the aldehyde (XX), or it may change conformation to the axially substituted diazonium ion (XIX). This diazonium ion (XIX) also has open to it two paths, namely, decomposition with loss of a proton and nitrogen to yield ultimately the cyclanone (XXII), or reversion to XVI. A similar course of reasoning may be applied to the conversion of the axial-amino conformation (XVIII) of the aminoalcohol which may be assumed to

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†The scheme represented in Fig. 1 for the conversion of XIX to the cyclanone (XXII) does not imply that this is the established sequence. An equally acceptable mechanism is the shift of a hydride ion from the hydroxyl-bearing carbon ejecting the nigrogen from the adjacent carbon similar to the way in which the carbon-carbon bond migration (XVI → XVII) must take place. This is followed by the removal of the proton remaining on the oxygen with the direct formation of the ketone and not the enol.

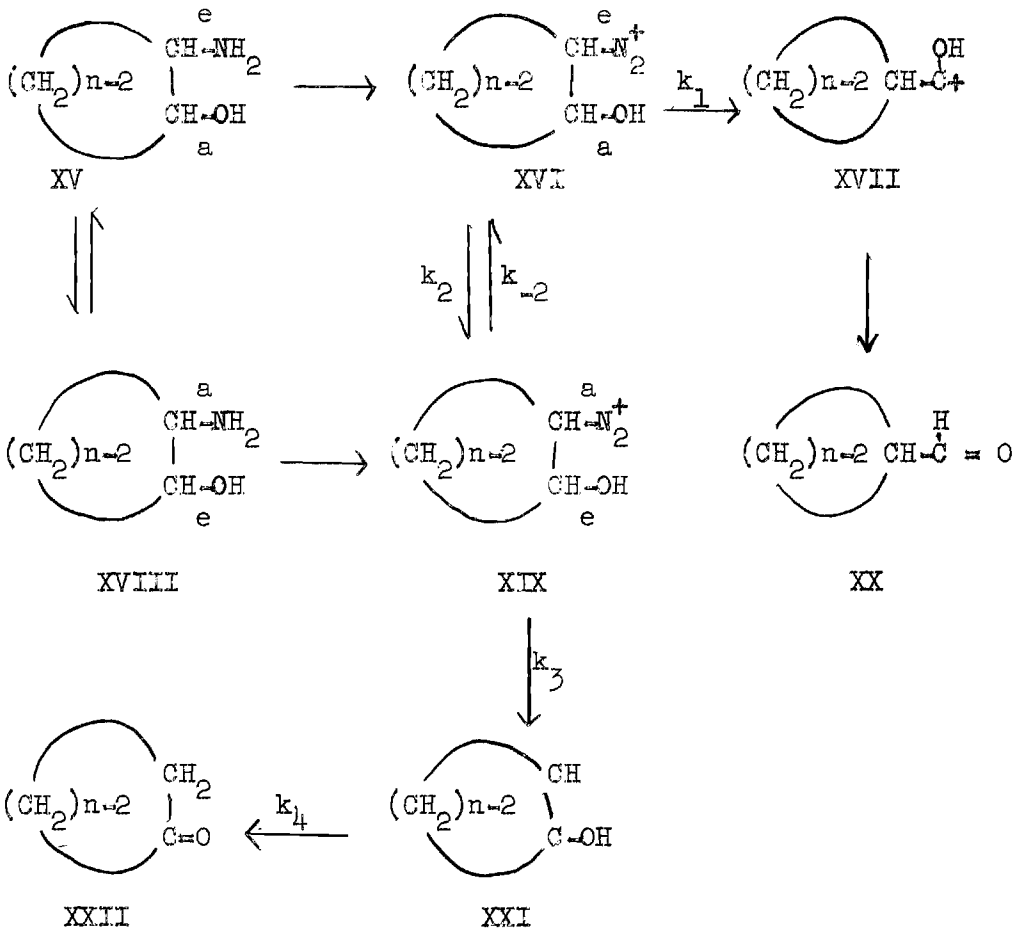


Fig. 1. Equilibria Involved in the Deamination of the cis-2-Aminocyclanols

be in equilibrium with XV.

In order to explain the course of the deamination of the cis-aminoalcohols, it is necessary to assume that the rate of the reaction to lose a hydrogen ion and nitrogen (XIX $\rightarrow$ XXI) is fast with respect to the movement of a ring bond (XVI $\rightarrow$ XVII). It must also be postulated that, because of the flexibility of the cycloheptane ring, the rate of equilibration of the two conformations of the diazonium ion from cis-2-aminocycloheptanol (XVI $\leftrightarrows$ XIX, n = 7) is much faster than the rate of equilibration between the two forms of the diazonium ion from cis-2-aminocyclohexanol (XVI $\rightleftarrows$ XIX, n = 6). As a result the ratio of rate constants, k_2/k_1, for n = 7 is larger than for n = 6. Assuming that k_{-2}/k_3 is relatively small because of the rotational barrier of cyclohexane, one would expect a greater proportion of rearranged product (XX) to be formed from cis-2-aminocyclohexanol than from cis-2-aminocycloheptanol.

A somewhat more rigorous treatment of the kinetic situation is set forth as follows: Assuming $k_4[XXI] \gg k_3[XIX]$ and $k_5[XVII] \gg k_1[XVI]$ then the rates of formation of the final products are essentially the same as the formation of their respective, immediate precursors. Therefore, if

$$v_{XVII} = k_1[XVI],$$

$$v_{XXI} = k_3[XIX],$$

$$K_e = [XIX]/[XVI] = k_2/k_{-2} \text{ and,}$$

$$[XIX] = k_2[XVI]/k_{-2}, \text{ then}$$

$$v_{XXI} = k_3k_2[XVI]/k_{-2} \text{ if equilibrium is rapidly established,}$$

i.e., if k_2 and $k_{-2} \gg k_1$ and k_3. In order for the ketone to predominate

as in the case of cis-2-aminocycloheptanol then

$$k_1[XVI] \ll k_2k_3[XVI]/k_{-2}[XIX] \text{ and}$$

$$k_1 \ll k_2k_3/k_{-2}[XIX].$$

If equilibrium is not rapidly established

$$k_2[XVI] \ll k_1[XVI] \text{ and}$$

$$k_{-2}[XIX] \ll k_3[XIX].$$

This corresponds to the case of cis-2-aminocyclohexanol in which the relative concentrations of the two conformers controls the product ratio.

III. EXPERIMENTAL

Infrared spectra were taken as liquid films or in chloroform solution on a Perkin-Elmer Model 137 Infracord Spectrophotometer. Analyses were performed for Galbraith Microanalytical Laboratories, Knoxville, Tennessee. All melting points are uncorrected and were taken either on a Fischer-Johns melting point block or on a Köfler hot stage.

Reduction of Cycloheptanone.--One hundred grams (0.89 mole) of cycloheptanone (Aldrich Chemical Co.) was dissolved in 300 ml. of methanol and cooled in an ice bath to 5 - 10°. A solution of 33.7 g. (0.89 mole) of sodium borohydride in 200 ml. of cold (5°) water was added slowly with a minimum of stirring. The temperature initially rose to 30° and was then maintained at 5 - 10°. The time required for the addition was 70 min. with the last 50 ml. being added rapidly with no rise in temperature. The reaction mixture was allowed to stand for 260 min. at 2° at which time a 2,4-dinitrophenylhydrazine test was negative. The reaction mixture was acidified with 500 ml. of 2.4N hydrochloric acid. After standing overnight, the organic layer was drawn off, and the aqueous layer was extracted with three portions of chloroform totalling 125 ml. The combined organic portions were dried and concentrated on a steam bath to ca. 125 ml. This crude product was used directly for conversion to cycloheptene.

Cycloheptene.--Crude cycloheptanol prepared by the reduction of cycloheptanone was used directly. Fifty two grams of crude cycloheptanol was added dropwise with stirring to a flask containing ca. 100 ml. of 85% phosphoric acid maintained at 135 - 155°; the cycloheptene steam distilled simultaneously at 82 - 95°. The aqueous layer of the distillate was separated and washed three times with ether. The combined organic layers were washed once with 10% potassium carbonate and dried over calcium chloride. The ether was carefully evaporated and the cycloheptene distilled at 107 - 110°, yield 18.7 g., 43%.

Cycloheptene Oxide.--Cycloheptene, 7.9 g. (0.082 mole), was added dropwise to 300 ml. of a chloroform solution of perbenzoic acid[47] prepared from 50 g. (0.206 mole) of recrystallized benzoyl peroxide. The solution was refrigerated for 24 hrs., washed with 10% potassium carbonate and 10% sodium bisulfite, and the chloroform was removed carefully on a steam bath. The product was distilled at 21 mm. pressure to yield a fraction boiling at 60 - 66°, yield 6.3 g., 68%.

trans-2-Aminocycloheptanol.--A 250 ml. pressure flask was charged with 6.00 g. (0.053 mole) of cycloheptene oxide, 30 ml. of concentrated ammonium hydroxide, and 18 ml. of 95% ethanol. The flask was sealed and heated in a steam jacket for 18 hrs. The reaction mixture was homogeneous at this temperature. The ethanol and water were removed on a steam bath at reduced pressure, and the product was distilled at 15 mm. pressure introducing nitrogen gas through a capillary to aid ebullition. The fraction boiling at 100 - 104° was collected, yield 3.90 g., 57%.

The distillate solidified completely on cooling, m. p. 71-72°. The trans-2-aminocycloheptanol was sublimed at 60° and 10 mm. pressure, m. p. 74 - 75°.

trans-2-(p-Nitrobenzamido)cycloheptanol.--To a solution of 3.90 g. (0.03 mole) of trans-2-aminocycloheptanol in 75 ml. of water was added a solution of 5.58 g. (0.03 mole) of freshly recrystallized p-nitrobenzoyl chloride in 70 ml. of dry benzene and 24 g. (0.03 mole of sodium hydroxide) of 5% aqueous sodium hydroxide. The heterogeneous mixture was shaken intermittently for 10 min. at room temperature, cooled in an ice bath, and filtered. The trans-2-(p-nitrobenzamido)cycloheptanol was crystallized from 95% ethanol yielding 6.60 g., 83%, of very pale yellow crystals, m. p. 190.5 - 191.5°.

Anal. Calc'd. for $C_{14}H_{18}N_2O_4$: C, 60.14; H, 6.53; N, 10.06. Found: C, 60.19; H, 6.73; N, 10.08.

2-p-Nitrophenyl-4,5-cis-cycloheptanoöxazoline.--To 6.60 g. (0.025 mole) of trans-2-(p-nitrobenzamido)cycloheptanol was added 11.3 g. (0.096 mole) of thionyl chloride. The flask was fitted with a calcium chloride tube and allowed to stand at room temperature for 12 hrs. A large excess of dry ether was added and the precipitated solid collected; crystallization from a mixture of ethanol-water afforded 3.0 g., 58%, of very pale yellow crystals. Several recrystallizations from aqueous ethanol gave 2-p-nitrophenyl-4,5-cis-cycloheptanoöxazoline, m. p. 120-121°.

Anal. Calc'd. for $C_{14}H_{16}N_2O_3$: C, 64.57; H, 6.19; N, 10.76. Found: C, 65.09; H, 6.08; N, 11.11.

cis-2-Aminocycloheptanol.--[33] Fifty milliliters of 4N hydrochloric acid was added to 6.0 g. (0.024 mole) of crude 2-p-nitrophenyl-4,5-cis-cycloheptanoöxazoline. The reaction mixture was boiled under reflux for 24 hrs., refrigerated for 12 hrs., and filtered. The filtrate was made alkaline with 20% sodium hydroxide and continuously extracted with ether for 24 hrs. The ethereal extract was evaporated leaving 2.40 g., 78%, of solid cis-2-aminocycloheptanol. A further 24 hr. extraction yielded only a negligible amount of solid. The cis-2-aminocycloheptanol was purified by sublimation at 70° and 10 mm. pressure to give white crystals, m. p. 81 - 82°.

Anal. Calc'd. for $C_7H_{15}N$: C, 65.07; H, 11.70; N, 10.83. Found: C, 64.64; H, 12.03; N, 10.91.

cis-2-(p-Nitrobenzamido)cycloheptanol.--The p-nitrobenzamide of cis-2-aminocycloheptanol was prepared in the manner described for trans-2-aminocycloheptanol, forming very pale yellow crystals from aqueous ethanol, m. p. 129 - 130°.

Anal. Calc'd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.11; H, 6.36; N, 10.25.

Deamination Procedures: (a) trans-2-Aminocycloheptanol.--A solution of 0.129 g. of trans-2-aminocycloheptanol in 1.0 ml. of glacial acetic acid and 2.0 ml. of water was chilled in a salt-ice bath. To this was added a cold sclution of 1.4 g. of sodium nitrite in 3.0 ml. of water, and the solution was allowed to stand in the cold for 30 min. The reaction mixture was made basic with 20% sodium hydroxide and

extracted with ether. The ethereal extracts were dried and the solvent removed on a steam bath through a short Vigreux column, affording 0.106 g. 96%, of yellow oil. This oil was treated with 2,4-dinitrophenylhydrazine in aqueous perchloric acid to give a yellow powder, m. p. 165 - 169°. Crystallization from ethanol-ethyl acetate gave yellow orange plates, m. p. 170 - 172°. A mixed melting point with the 2,4-dinitrophenylhydrazone of cyclohexanecarboxaldehyde showed no depression.

(b) cis-2-Aminocycloheptanol.--A solution of 0.135 g. of cis-2-aminocycloheptanol in 3.0 ml. of water and 1.0 ml. of glacial acetic acid was chilled in a salt-ice bath. To this solution was added a cold solution of 1.0 g. of sodium nitrite in 3.0 ml. of water. The reaction mixture was allowed to stand in the cold for 30 min., made basic with 20% sodium hydroxide, and extracted with two portions of ether. The ethereal extract was dried and the solvent removed on a stream bath through a short Vigreux column to give 0.073 g., 62%, of oil which was converted to the 2,4-dinitrophenylhydrazone, obtained as a yellow powder, m. p. 142 - 145°. Several crystallizations from ethanol gave yellow crystals, m. p. 147 - 148°, undepressed upon admixture with an authentic sample of cycloheptanone 2,4-dinitrophenylhydrazone.

Treatment[48] of another deamination mixture of the cis-aminoalcohol with dimedone solution gave the dimedone derivative of cyclohexanecarboxaldehyde in 16% yield, m. p. 176 - 179°, which upon admixture with the same derivative of authentic cyclohexanecarboxaldehyde showed no depression in melting point. The preparation of the dimedone derivative of a known amount of cyclohexanecarboxaldehyde afforded a 45% yield of this

derivative. Consequently, according to this data the deamination mixture contained 36% cyclohexanecarboxyaldehyde.

Cyclohexanecarboxaldehyde.--Cyclohexanecarboxaldehyde was prepared according to Wood and Comley[34] from 10.0 g. (0.061 mole) of cyclohexyl bromide and 9.26 g. (0.063 mole) of ethyl orthoformate. The product was distilled yielding 1.6 g., 23%, of cyclohexanecarboxaldehyde.

The 2,4-dinitrophenylhydrazone was prepared, m. p. 170 - 172°. The reported melting point for this derivative is 173°.[49]

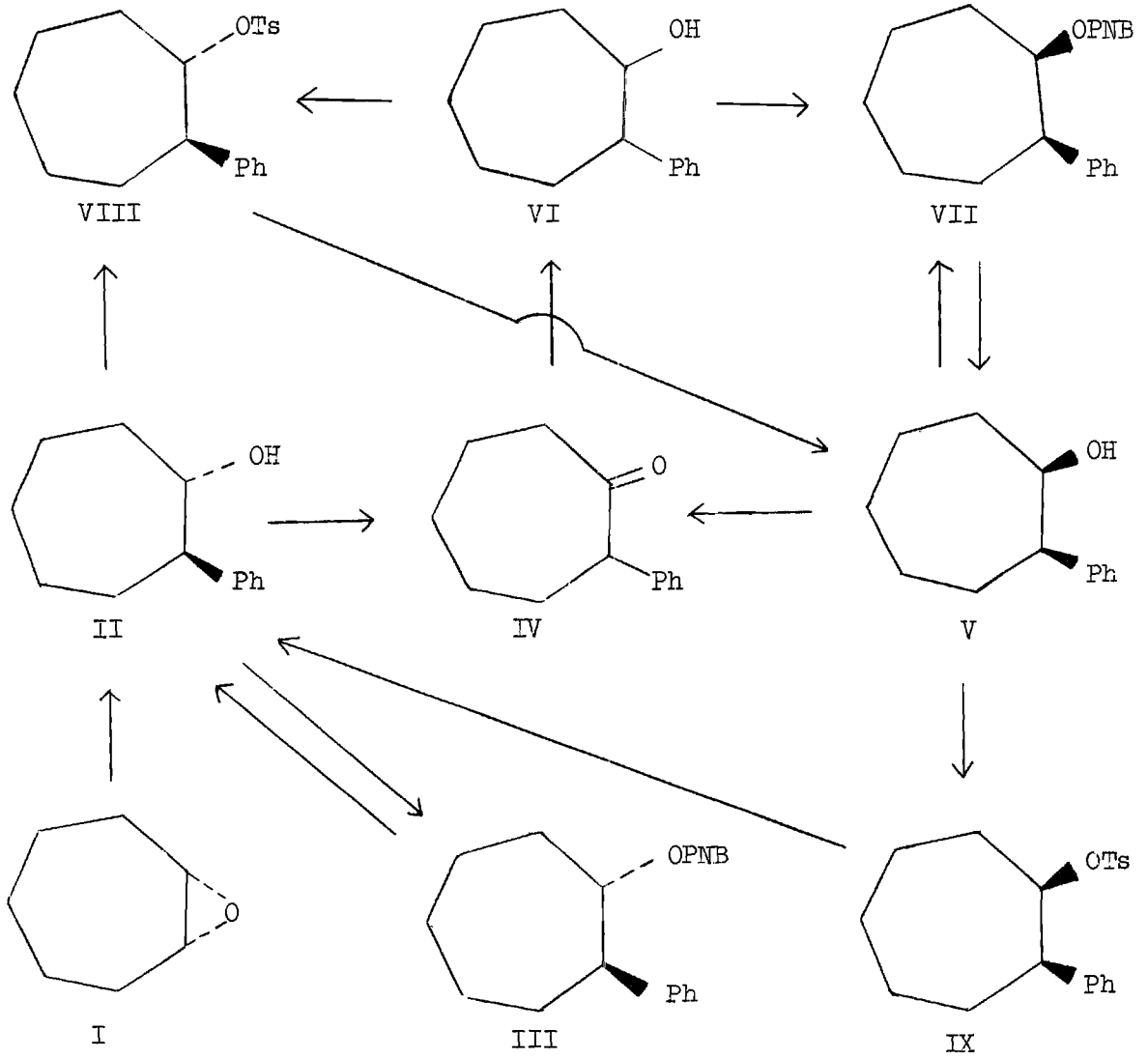
IV. DISCUSSION:

DEHYDRATION OF CIS- AND TRANS-2-PHENYLCYCLOHEPTANOL

In order to prepare both cis- and trans-2-phenylcycloheptanol with unequivocal stereochemistry, it was necessary to select a reaction sequence which afforded at least one of the stereoisomeric alcohols pure and of known configuration. The other epimer could then be isolated from a mixture of the two with no ambiguity of structure.

A method which provided a stereospecific route to trans-2-phenylcycloheptanol was that of Cook, Hewett, and Lawrence.[50] These workers have prepared trans-2-phenylcyclohexanol by the diaxial opening of cyclohexene oxide with phenyllithium. It is noted here that reaction of cyclohexene oxide with ordinary Grignard reagents gives anomalous rearrangements[51] which dictates the use of the organolithium compound. Following this procedure, cycloheptene oxide (I) was treated with an ethereal solution of phenyllithium to provide trans-2-phenylcycloheptanol (II) as a colorless oil, b. p. 113 - 114° at 0.5 mm. pressure. The p-nitrobenzoate ester (III) was prepared and found to melt at 84.0 - 85.0°. In order to show conclusively that no unusual rearrangement had been induced by phenyllithium during the reaction, a portion of the trans alcohol was oxidized with Kiliani's reagent[52] (chromic oxide-sulfuric acid) to afford 2-phenylcycloheptanone (IV). The 2,4-dinitrophenylhydrazone melted at 168.5 - 171.5°[53,54] after one crystallization and did not depress the melting point of an authentic sample. It was noted that

the desired trans-2-phenylcycloheptanol was produced only in runs where an excess of cycloheptene oxide was present. If an excess of phenyllithium were used an alcohol was obtained which boiled at approximately the same temperature as the desired product but which did not form a solid p-nitrobenzoate ester. The 3,5-dinitrobenzoate was, however, solid and crystallized well, melting at 100°. This material was not investigated further.



With one of the pair of stereoisomeric alcohols synthesized and characterized the stereochemical requirements to prepare the other, cis-2-phenylcycloheptanol (V), were not necessarily so stringent. Several routes were available which seemed to present the possibility of obtaining the cis alcohol in mixture with the trans isomer. The more obvious methods were among the wealth of reduction procedures, both catalytic and metal hydride. The availability of 2-phenylcycloheptanone[55] enhanced the appeal of this route. In connection with 2-phenylcycloheptanone it is interesting to note that in the preparation of the 2,4-dinitrophenylhydrazone derivative two solid products were observed, one yellow-orange and the other red. The yellow-orange solid was obtained by crystallization from ethanol-ethyl acetate and melted properly.[53,54] In view of the fact that gas chromatography showed the ketone to be homogeneous it seems plausible that the red material was the less stable syn form of the derivative. This behavior was quite reproducible and was observed with samples of the ketone from totally different sources. Ginsburg and Pappo report the isolation of two forms of the 2,4-dinitrophenylhydrazone of 2-phenylcyclohept-2-enone.[53]

Catalytic hydrogenation of the ketone, under the proper conditions, should proceed by addition of hydrogen from the catalyst surface to the least hindered side of the carbonyl group to afford the cis alcohol as the major product.[56] In our hands, however, 2-phenylcycloheptanone did not yield a suitable product by catalytic hydrogenation. A number of reductions were carried out at room temperature and atmospheric pressure using various solvents and catalysts, and in no case, where the absorption of hydrogen proceeded at a reasonable rate, was exclusive

reduction of the carbonyl group obtained. In glacial acetic acid or acidic ethanol reduction of the benzene ring took place at a rate comparable to that of the carbonyl group. This was shown by the fact that there was no decrease in the rate of hydrogen uptake after one mole had been absorbed and that considerable ketone remained after reduction. Under neutral conditions, reduction proceeded very slowly, and, although the decreased acidity of the solvent should preclude reduction of the aromatic ring, the extended reaction time required would not favor the production of the less stable cis isomer. Some variation in catalyst (platinum on carbon, palladium on carbon, and platinum oxide), while affecting the rate of reaction, did not apparently improve the selectivity towards the carbonyl group.

The catalytic hydrogenation route was abandoned and the reduction with complex metal hydrides was pursued. The recent availability of complex metal hydrides and their proven usefulness as versatile, selective, and clean reducing agents has brought them under intensive study.† The factors influencing their stereospecificity are not fully understood, but Wheeler and Huffman,[58] by consideration of the apparent species in solution have offered a hypothesis which consolidates known data.[59]

2-Phenylcycloheptanone can produce either cis- or trans-2-phenylcycloheptanol depending upon the direction from which the hydrogen is added to the carbonyl group. It was necessary to choose, by analogy, a metal hydride which should react with 2-phenylcycloheptanone to produce

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†See ref. 57 and citations therein for summaries concerning complex metal hydride reductions.

predominantly the cis alcohol, and the work of Hardy and Wicker[60] on a number of methylcyclohexanones seemed to provide the necessary model. Potassium borohydride produced 59% of cis-2-methylcyclohexanol from the corresponding ketone. However, reduction of 2-phenylcycloheptanone with this reagent was given up because complete reduction was not obtained. Several other borohydrides were tried briefly with the same results. These results as well as the difficulty of catalytic hydrogenation testify to the hindered nature of the carbonyl group in 2-phenylcycloheptanone.

With another route in mind, vide infra, and because of the quantity of ketone available, a reduction with lithium aluminum hydride was carried out in which the reaction time was 70 min. in the cold. This again afforded only partial reduction. However, the p-nitrobenzoate ester of the crude product (VI) was prepared and purified by crystallization from ethanol to a constant melting material, m.p. 92.0 - 93.2°. The isolated material was shown to be cis-2-phenylcycloheptyl p-nitrobenzoate (VII) by saponification to the alcohol (V) the infrared spectrum of which was significantly different from that of the known trans alcohol. Oxidation of V to 2-phenylcycloheptanone furnished conclusive evidence that, indeed, the p-nitrobenzoate of the cis alcohol had been isolated. Vapor phase chromatography of the product mixture from the reduction showed only two major components. It was possible, however, by infrared spectroscopy to obtain the percentage of ketone present and, this by difference from the vapor phase chromatography data, the amount of cis alcohol was determined. These percentages are given in Table 2. The results of this reaction were quite reproducible, being conducted several times

Table 2. Reduction of 2-Phenylcycloheptanone -- Product Composition

Reduction Method	Percentage of Component		
	Cis Alcohol	Trans Alcohol	Ketone
LAH-70 min.	63.8	13.4	18.6
LAH-$AlCl_3$ †	12.9	52.3	21.8

†Five unidentified products detected by gas chromatography constitute the remaining 13.0%.

to obtain a quantity of cis-2-phenylcycloheptanol. It is well-established by numerous examples[57] that the reduction of ketones with lithium aluminum hydride affords predominantly the more stable epimer. It is seen then that the reduction of 2-phenylcycloheptanone is in direct contrast to the majority of other data.

In attempting to improve the yield by complete reduction of the ketone a second set of conditions were used in which the reaction mixture was boiled under reflux for an extended period of time. In this instance the p-nitrobenzoate ester of the cis alcohol could not be obtained from the crude derivative by crystallization as it was from the short reduction product, and indeed, one run afforded trans-2-phenylcycloheptyl p-nitrobenzoate after several crystallizations. The product ratios were not determined by vapor phase chromatography for these extended reductions.

Carrying this investigation further to determine whether the trans alcohol was obtainable by reduction of the ketone, a recent publication by Eliel and Rerick[60] indicated that a "mixed hydride" reduction should lead predominantly to trans-2-phenylcycloheptanol. Equilibration of a

number of epimeric 4-alkyl cyclohexanols to the more stable epimer with a mixture of lithium aluminum hydride and aluminum chloride in the presence of excess ketone was remarkably successful. Treatment of 2-phenylcycloheptanone under these conditions yielded a mixture from which the p-nitrobenzoate ester of the trans alcohol could not be easily obtained by crystallization, however, it was shown by a combination of vapor phase chromatography and infrared spectroscopy, as previously described, that the trans alcohol was present in a four-fold excess over the cis epimer (Table 2).

In order to rationalize these results one may look more closely at the postulates of Wheeler and Huffman.[58] Lithium aluminum hydride is considered to be capable of two types of dissociation, i.e.,

$$LiH + AlH_3 \rightleftharpoons LiAlH_4 \rightleftharpoons Li^{+1} + AlH_4^{-1}$$

The usual observation that the more stable epimer is produced by reduction with lithium aluminum hydride is attributed to the initial, fast attack of the species AlH_3, a Lewis acid, on the carbonyl group forming a complex such as XVII followed by the slow addition of hydride by a suitable species to form XIV. Examination of the complex (XVII or XVIII) reveals that the oxygen-bearing carbon must be trigonal; this is demanded by both of the contributing resonance structures of the conformations of the complex (XVIIa, XVIIb, XVIIIa, and XVIIIb). Strictly in terms of the complex of 2-phenylcycloheptanone, the fast addition of aluminum hydride, AlH_3, to the equilibrium mixture (X $\rightleftarrows$ XI) will afford a predominance of complex XVII because X is the more stable conformation of the ketone. There are three modes of reaction open to XVII besides reversion to the ketone;

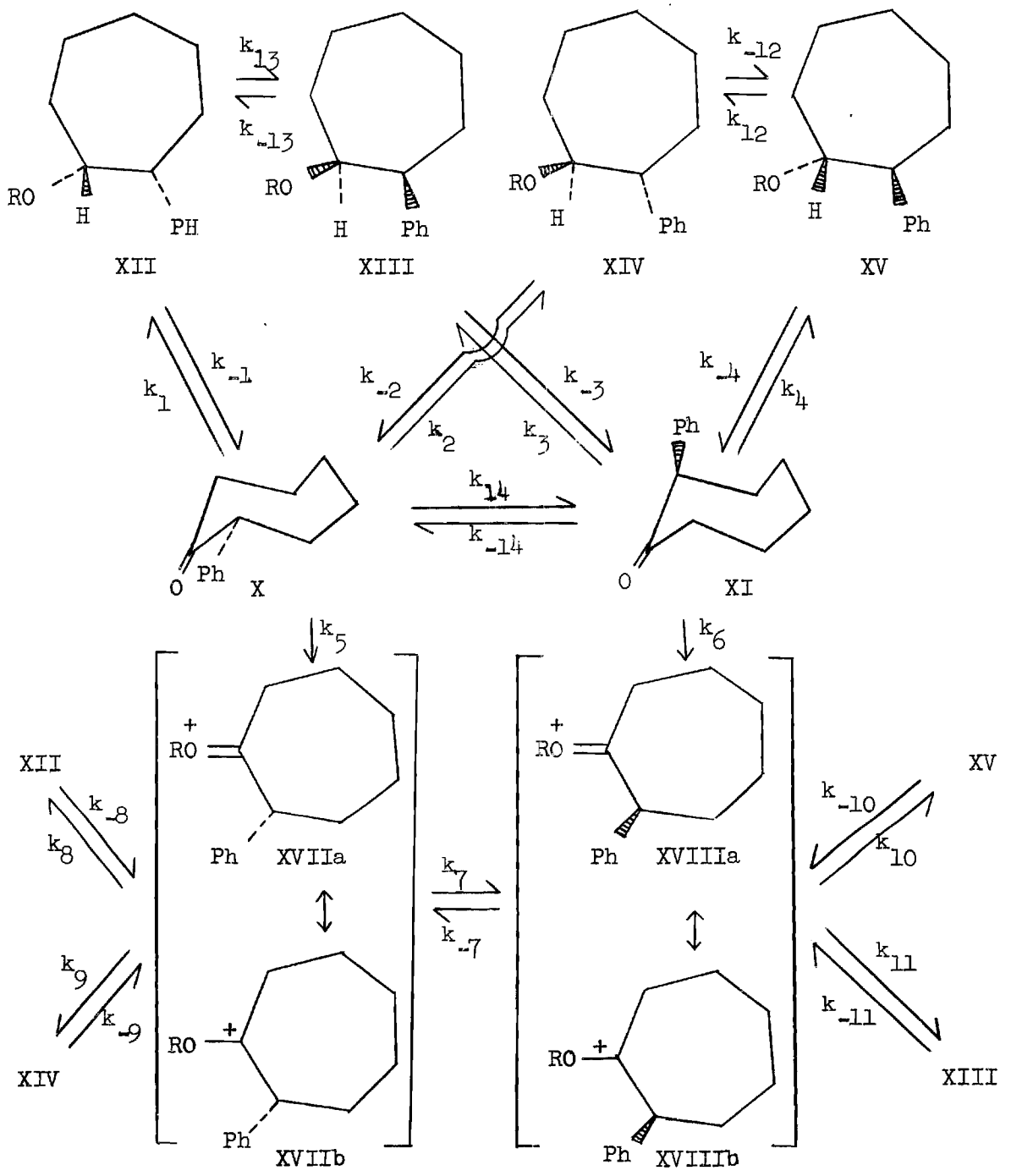

Figure 2†. Equilibria Involved in the Reduction of 2-Phenylcycloheptanone.

†R = $(-AlH_3)^{-1}$ or a species subsequently derived from this group.

the complex can change conformation to XVIII, undergo attack by hydride donor affording XII, or undergo a similar attack producing XIV. The conformer XVIII has the same opportunities open to it; reversion to the ketone, inversion to XVII, hydride attack forming XIII or XV. The two fruitful reaction paths as far as production of the observed cis alcohol are those which lead to XII or XIII. The most attractive of these alternatives is the direct production of XII for two reasons. First of all, the immediate precursor to XII is the more stable of the two conformations of the complex by virtue of having the pheryl group quasi-equatorial, therefore, it should be present in the highest concentration. Secondly, the attacking hydride species should be able to approach XVII from a quasi-equatorial direction to form XII with much more facility than a similar reagent would be able to approach XVIII from a quasi-axial direction. The alternate mode in which lithium aluminum hydride can dissociate, vide supra, provides two more ways in which the cis alcohol can be formed. Direct attack by aluminum hydride ion, AlH_4^{-1}, on X can form either XII or XIV; the same attack on XI will produce XIII or XV. It is possible to choose between the possibilities on the same grounds as before. The cis alcohol is produced either by quasi-equatorial attack on X or quasi-axial attack on XI. The former of these seems more likely again because of the greater concentration of X and the lessened steric hindrance offered to a quasi-equatorial approach. As stated, it was not possible to purify the cis alcohol by means of the p-nitrobenzoate ester if the reduction mixture was heated for a prolonged period in contact with excess lithium aluminum hydride. From this it is concluded that a significant amount of epimerization must have taken

place by some route during the extended reaction time, converting the less stable cis alcohol to the more stable trans isomer. Conversion of the cis alcohol in the form of XII or XIII to the trans alcohol (XIV or XV) can proceed by several routes two of which are; the concerted, one-step decomposition of XII or XIII directly back to the ketone, albeit unlikely because of the strength of aluminum-oxygen bonds, or removal of a hydride ion from XII or XIII to form the respective complex. The ketone or complex then has open to it all of the possibilities mentioned previously. In consideration of these two modes of reversal the principle of microscopic reversibility restricts our choice of modes of decomposition of the cis alcohol depending upon the assumed route of formation. That is, simply, if the least energetic method of formation of the cis alcohol is through a complex such as XVII or XVIII then this also must be the most favored path whereby it reverts to the starting material. This is similarly true for the direct addition of aluminum hydride ion to the ketone, if the cis alcohol is formed most easily by this mechanism, then regeneration of the ketone also follows this path in reverse. Regardless of whichever process predominates, i.e., which set of equilibria may apply to the epimerization of cis to trans, the underlying reason for the increase in concentration of the trans isomer is its greater stability. In other words, k_{-12}, k_{-2}, and k_{-9} are all small enough so that despite the increase in concentration of XIV its rate of reaction will be slow. This apparent epimerization of isomeric alcohols is in contrast to the studies of Eliel and Rerick[61] and, while the facts at hand cannot be denied, further investigation is certainly indicated. A singular possibility is that a Meerwein-Ponndorf-Verley -- Oppenauer type of equilibrium

is established through the agency of dissolved atmospheric oxygen or some other oxidant. Doering and Aschner[62] have cited numerous examples in which an optically active alcohol is not racemized in the presence of a strong base alone, but that in addition a reversible oxidation system is required. Even though this type of equilibration is slow the contact time of our reaction would have been sufficient for considerable epimerization to take place.

The formation of the p-toluenesulfonate esters was carried out concurrently with the preparation of the p-nitrobenzoate esters of the various reduction products of 2-phenylcycloheptanone. The purpose was to obtain trans-2-phenylcycloheptyl p-toluenesulfonate (VIII) which upon treatment with basic alumina would afford the cis alcohol according to the procedures of Douglas, et al.,[63] and Chang and Blickenstaff.[64] The product resulting from a 70 min. reduction of 2-phenylcycloheptanone was treated with p-toluenesulfonyl chloride, and in contrast to the later proven preponderance of cis-2-phenylcycloheptanol, crystallization of the crude tosylation mixture from cyclohexane afforded, in poor yield, trans-2-phenylcycloheptyl p-toluenesulfonate. A large solubility difference between cis- and trans-2-phenylcycloheptyl p-toluenesulfonate must account for the isolation of the trans isomer when it is present only in small amounts. This solubility difference was determined in cyclohexane and is quite remarkable; the cis tosylate is soluble to the extent of 185 mg./ml. at 60° while the limit of solubility of the trans derivative is 9 mg./ml. at this temperature. The difference in the solubilities of cis- and trans-2-phenylcycloheptyl p-nitrobenzoate while noticible was not nearly so great.

trans-2-Phenylcycloheptyl p-toluenesulfonate is a moderately unstable compound, much more so than the cis isomer, as shown by the decomposition of the trans tosylate at the melting point whereas the cis tosylate melt becomes heterogeneous only above 100°. Crystallization from ethanol caused erratic melting point behavior of the trans tosylate. In some instances spontaneous decomposition to a purple substance at room temperature occurred when the crystals were in contact with the mother liquor or even after drying. The analyses are poor for both tosylates perhaps because it was not possible to dry them at elevated temperatures. The carbon and hydrogen percentages are calculated on the basis of a dihydrate for which the agreement is fair.

In accord with the previous studies on steroidal tosylates,[63,64] trans-2-phenylcycloheptyl p-toluenesulfonate upon reaction with basic alumina afforded the cis alcohol in moderate yield. The product was identified as cis-2-phenylcycloheptanol by comparison of the infrared spectrum with that of the authentic alcohol (the spectra were identical in every respect) and by the melting point and mixed melting point of the p-nitrobenzoate ester. In addition cis-2-phenylcycloheptyl p-toluenesulfonate (IX) upon similar treatment also underwent inversion with the formation of the trans alcohol, identified as before by the infrared spectrum and the p-nitrobenzoate derivative. The fact that inversion is observed in the case of the trans alcohol is significant in that the phenyl group does not participate as a neighboring group even though its situation is favorable for such participation.

Phosphorus oxychloride, thionyl chloride, and, to a limited extent, p-toluenesulfonyl chloride have proved to be very useful as dehydrating

agents for organic alcohols. Their utility stems from the fact that the reaction conditions are mild (0-100°); the reagent is not acidic when used in conjunction with pyridine which permits the isolation of unstable olefins; and the dehydration proceeds *via* a mechanism whereby the accurate prediction of products is possible insofar as the stereochemistry of the substrate alcohol is known. As is frequently the case, reagents with the general characteristics of stereospecificity and moderate reaction conditions have found a great deal of utility in the steroid[65] and similar fields. In steroid molecules where each substituent is held in a fixed orientation, the stereochemical requirements for reactions can be established by employing appropriately substituted molecules of varying configuration. In the case of phosphorus oxychloride and other similar acid chlorides cursory examination reveals that there would appear to be several mechanisms by which these reagents could effect the dehydration of an alcohol.[66] There is the possibility of *anti*- or *syn*-parallel elimination coupled with the possible inversion or retention of configuration of the hydroxyl-bearing carbon because of attack by a halide species. These variations have characteristic stereochemical requirements and in the cyclohexane series these requirements are firmly correlated with configuration and conformation.

It is of interest here to review the findings of Sicher, *et al.*[18,19†] The ability of larger ring systems, particularly the seven-membered ring, to adapt themselves to both *anti*- and *syn*-parallel mechanisms was clearly demonstrated in these studies. Phosphorus oxychloride chloride dehydrations are certainly firmly established as proceeding through a structure

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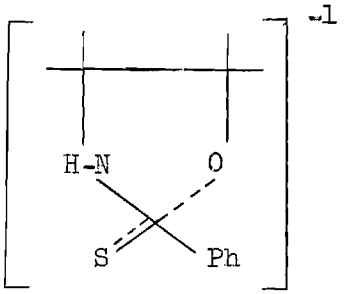
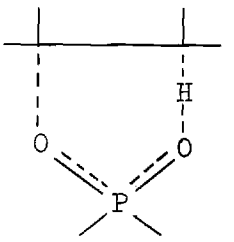
†See Introduction for a previous discussion of this work.

in which the leaving groups are diaxial, however, the systems which support this stereochemical restriction are inflexible molecules, and this intrinsic molecular rigidity may preclude the possibility of a less favorable (or more favorable if the geometry were appropriate) mechanism competing. A mechanism involving a transition state similar to B, that for the cyclization of the thiobenzamido alcohols, is represented by C. This as well resembles the Chugaev reaction (thermal decomposition of



B



C

xanthates) and ester pyrolyses in general. Considering the fact that cis-2-thiobenzamidocycloheptanol cyclizes faster than the cis cyclohexane derivative by a factor of 152[19] and that the rate ratio, 423,[19] for the two trans compounds is even greater, a competitive syn-elimination of water induced by phosphorus oxychloride would seem possible for cycloheptanol derivatives.

Reactions in the steroid field,† however, do clearly indicate that, whatever the intermediates may be, phosphorus oxychloride-pyridine dehydrations result in the trans elimination of the elements of water. Conversions which exemplify this fact are: The reaction of 7α-hydroxycholestanyl acetate (XXVI) with phosphorus oxychloride in pyridine gives

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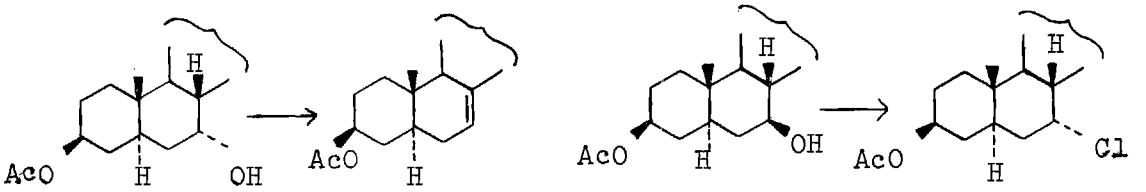
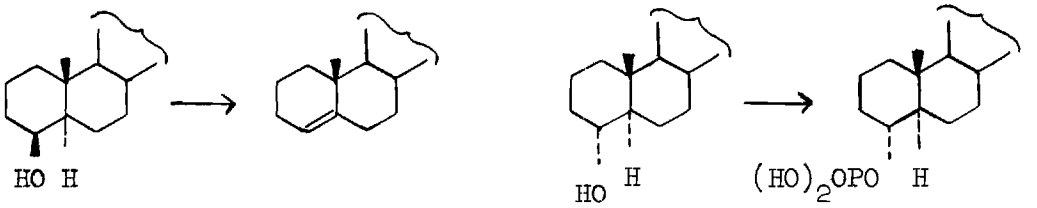
†For examples in addition to those cited see ref. 65.

Δ^7-cholestanyl acetate (XXVII), whereas the C-7 epimer, 7β-hydroxycholestanyl acetate (XXVIII) does not undergo dehydration but, instead, forms 7α-chlorocholestanyl acetate (XXIX).[67] In the absence of pyridine as well the same overall result, i.e., trans elimination, prevails. Thus, cholestane-4β-ol (XXX) upon treatment with phosphorus oxychloride alone affords Δ^4-cholestene (XXXI), while cholestane-4α-ol yields (XXXII) only the phosphate ester, cholestanyl-4α phosphate, (XXXIII).[68]

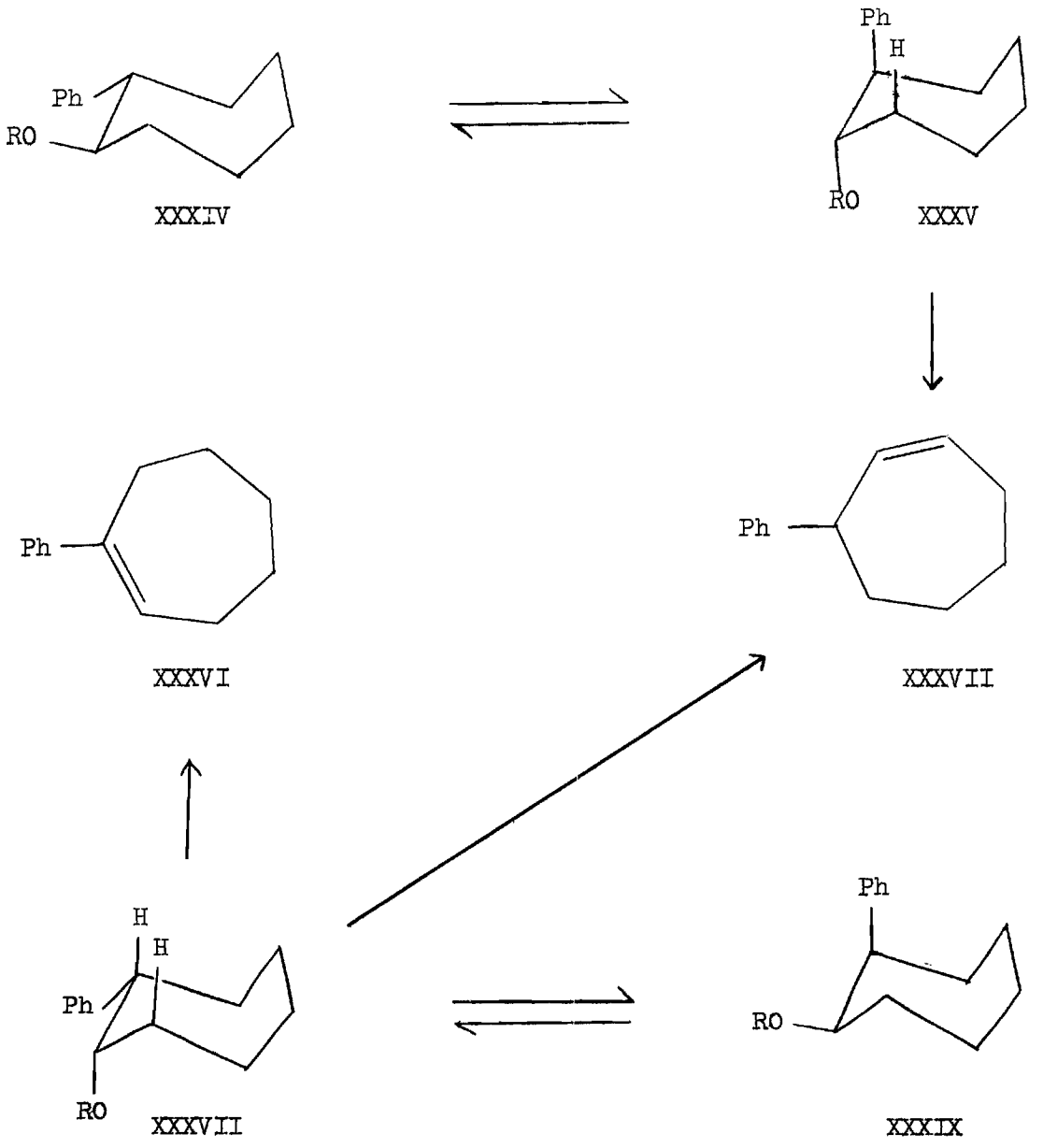


XXVI XXVII XXVIII XXIX



XXX XXXI XXXII XXXIII

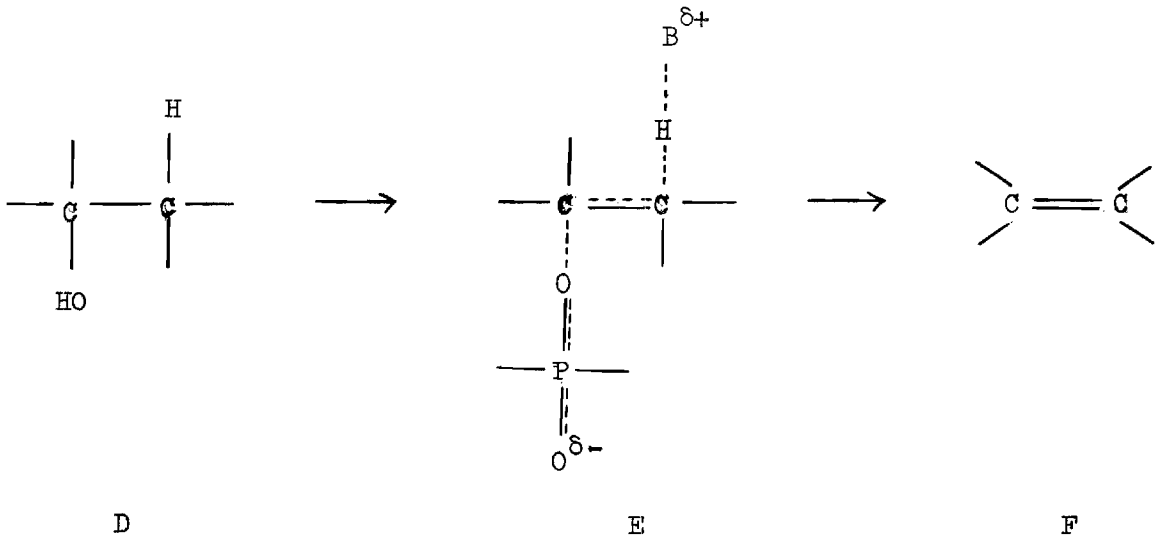
Ignoring any possible deviation from the accepted trans elimination mechanism for phosphorus oxychloride dehydrations, it would seem worthwhile to apply these reactions to a system wherein the spatial arrangement of the atoms is not well-established so that the products could be correlated to the conformation of the reacting species. The intention was to determine the ratio of 1- and 3-phenylcycloheptene resulting from cis-2-phenylcycloheptanol and trans-2-phenylcycloheptanol in order to further elucidate the stereochemistry of the



cycloheptane ring in terms of reaction characteristics of the cyclohexane ring. A systematic study of phosphorus oxychloride-pyridine dehydrations of the analogous monocyclic six-membered ring compounds has not been carried out, therefore it must be assumed that <u>trans</u> elimination would prevail in these systems as it does in the steroid molecules. An

abundance of evidence concerning other elimination reactions supports this assumption that there is little difference between flexible monocyclic six-membered ring systems and the larger fused cyclohexano systems except for those variations dictated by a difference in rigidity.† One pertinent example is that the Chugaev reaction of cis- and trans-2-phenylcyclohexyl xanthates has been carried out with the expected results.[69]

The most stable conformation of trans-2-phenylcycloheptanol should be XXXIV (R = H), which is in equilibrium with a second, much less favored conformation (XXXV, R = H) in which the substituents are located quasi-diaxial. If we assume that the sequence D → E → F represents the gross features of the dehydration, then XXXIV (R = -OPO) and XXXV (R = -OPO) will result from the initial addition of phosphorus oxychloride to the trans alcohol. The structure XXXIV (R = -OPO) is



D E F

†For a discussion of olefin-forming elimination reactions in general, including dehydrations, see ref. 70.

incapable of any such elimination as depicted in D → E → F because of the absence of an anti-parallel hydrogen, however the less stable conformer (XXXV, R = -OPO) does have a hydrogen situated in the proper orientation for trans elimination, and reaction via this route will lead to the unconjugated olefin, 3-phenylcycloheptene (XXXVII) as the exclusive product. Examination of the stereoisomeric cis-2-phenylcycloheptanol shows that there are two conformations of reasonable stability (XXXVIII and XXXIX). With the free hydroxyl present in the molecule (R = H) the more stable of the two is (XXXVIII), but esterification as the first step of the reaction leaves the question of relative conformational stability in doubt. This, however, is unimportant because, as in the trans alcohol, only one of the conformations can lead to reaction by a trans elimination of the elements of water; this is structure XXXVIII(R = -OPO). The trans removal of a hydrogen and the phosphate ester group from XXXVIII can, in this case, yield two different olefins, 1-phenylcycloheptene (XXXVI) as well as XXXVII.

Our studies have produced evidence that the phosphorus oxychloride-pyridine dehydration of cis- and trans-2-phenylcycloheptanol proceeds by the established trans elimination path. The dehydrations were carried out by dissolving the cyclanol in pyridine and then adding phosphorus oxychloride and warming for a short period of time. The reaction was remarkably clean, producing a practically colorless oil. This is in direct contrast to a series of thionyl chloride dehydrations conducted under identical conditions, which produced a brown mud-like mixture. A yellow oil was isolable from these dehydrations in poor yield, and it is of interest to note that there was no absorption maximum at

247 mμ displayed by any of the mixtures. The end-absorption was higher in these cases than for the phosphorus oxychloride dehydrations. This method of dehydration was not pursued further. The oil produced by the phosphorus oxychloride dehydration showed no hydroxyl absorption in the infrared region [71] and was analyzed for conjugated olefin by means of ultraviolet spectroscopy (Table 3). 1-Phenylcycloheptene was prepared by a known route[72] and was found to have a maximum absorption in the ultraviolet at 247 mμ (ϵ = 14,000), which is in agreement with the reported value.[72] All of the dehydration mixtures which did absorb between 285 and 225 mμ showed only one maximum and this occured at the absorption maximum of 1-phenylcycloheptene. The extinction of the dehydration mixtures at 247 mμ was used to estimate the percentage of conjugated olefin as 1-phenylcycloheptene. In addition the dehydration mixtures were also analyzed by vapor phase chromatography (see Chapter V, "Experimental," for conditions), and it was discovered that major portion of the product corresponded to neither 1-phenylcycloheptene nor 3-phenylcycloheptene (Table 3). As can be seen the unidentified products constitute 51.1% of the material obtained from the cis alcohol and 67.0% of the material from the trans alcohol. In an attempt to identify these constituents the following facts are considered: The dehydration mixture as a liquid film showed no hydroxyl absorption in the infrared. There was no maximum in the ultraviolet between 285 and 225 mμ for the dehydration product from the trans alcohol, and the ultraviolet maximum for the product from the cis alcohol occurred at 247 mμ corresponding to 1-phenylcycloheptene. The percentage of 1-phenylcycloheptene calculated from the extinction at this wavelength is in good

Table 3. Phosphorus Oxychloride Dehydrations of cis- and trans-2-Phenylcycloheptanol in Pyridine.

Alcohol	Product Determined by Vapor Phase Chromatography	Percentage Retention Weight	Retention Time (min.)
cis	3-Phenylcycloheptene	8.1	5.9
	1-Phenylcycloheptene	40.8	6.9
	Unidentified	6.9	10.0
	Unidentified	41.6	14.4
	Unidentified	2.6	15.9
trans	3-Phenylcycloheptene	32.1	5.8
	1-Phenylcycloheptene	2.0	6.9
	Unidentified	~ 1.5	9.9
	Unidentified	~ 0.8	12.0
	Unidentified	~ 1.7	14.2
	Unidentified	62.0	15.7
	Mole Percent of Conjugated Olefin as 1-Phenylcycloheptene Determined by the Extinction at 247 mμ.		
cis		37	
cis		37	
cis		39	
trans		~ 0	
trans		~ 0	
trans		~ 0	

agreement with the amount indicated by vapor phase chromatography. In addition hydrogenation of the product mixture from the trans alcohol with platinum on carbon in 95% ethanol resulted in absorption of one-third of a mole of hydrogen corresponding approximately to the amount of 3-phenylcycloheptene determined by vapor phase chromatography. The material isolated from the dehydrations was not soluble in water or aqueous sodium hydroxide. From this evidence it is concluded that the major constituent of the unidentified products does not contain a hydroxyl group, an olefinic linkage, or a phosphate ester group. Consideration of the

species present under the reaction conditions provides at least two other possibilities: 2-phenylcycloheptyl chloride (cf. XXVIII → XXIX) or an ether resulting from the bimolecular attack of the free alcohol on the phosphate ester derived from the alcohol. The extended retention time of the unknown materials would indicate that the higher molecular weight ether is a reasonable choice, but the formation of an ether by such a route is apparently unique in phosphorus chemistry. In the absence of other data no real choice can be made. Of course, both the chloride and ether could be formed as diastereoisomers which would account for the smaller amounts of materials with slightly different retention times and would also explain the difference in the retention times of the major non-olefinic products from the two alcohols, their being diastereoisomeric.

The formation of these other materials is significant in the case of cis- and trans-2-phenylcycloheptanol and should certainly be the subject of further investigation. However, equally important is the original object of the investigation, the ratio of 1- and 3-phenylcycloheptene obtained in the dehydrations. These ratios, if considered separately from the other, unknown products, are in accord with similar reactions of cyclohexane derivatives and support the scheme proposed (D → E → F) for the conformational requirements of phosphorus oxychloride and pyridine in the dehydration of cis- and trans-2-phenylcycloheptanol. The trans alcohol affords virtually no conjugated olefin (XXXVI) because in XXXV loss of hydrogen by an anti-parallel mechanism can only occur to give XXXVII. The production of a preponderance of XXXVI over XXXVII from the cis alcohol (XXXVIII) even though the situation of α-hydrogens is favorable for

the formation of both is rationalized on the basis that the removal of the more acidic benzyl hydrogen forming XXXVI is easier than removal of the hydrogen necessary to form XXXVII. And apparently the formation of XXXVII takes place with sufficient difficulty so that other alternate reaction paths can compete successfully with it, e.g., the formation of the unidentified products. It seems reasonable to assume that 3-phenylcycloheptene (XXXVII) is fairly stable at least with regard to isomerization to 1-phenylcycloheptene (XXXVI), under the reaction conditions, because of the results in the case of the trans alcohol, i.e., the detection of 32.1% 3-phenylcycloheptene in the presence of only 2.0% 1-phenylcycloheptene. The possibility that 3-phenylcycloheptene is isomerized to the conjugated olefin which then undergoes polymerization to a large extent is rendered unlikely by the fact that treatment of the phosphorus oxychloride dehydration product of trans-2-phenylcycloheptanol (containing ca. 32% of 3-phenylcycloheptene) with phosphoric acid afforded a mixture which contained ca. 25% of 1-phenylcycloheptene. This can be construed as representing a 78% conversion.

Phosphoric acid, although widely employed as a dehydration agent, has not been studied to determine the nature of the species present during the dehydrations. Some work has been carried out, however, on the stereochemical nature of the process, and of particular interest are the results of Price and Karabinos[29] who carried out the dehydration of cis- and trans-2-phenylcyclohexanol. They reported that the cis alcohol yielded a mixture of 1- and 3-phenylcyclohexene with the former predominating, while the trans alcohol furnished again a mixture but in this instance the non-conjugated olefin was the major product. They also

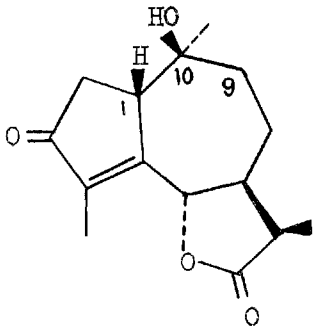
state that 3-phenylcyclohexene is not isomerized by the action of hot phosphoric acid. Subsequent investigation of the same reaction by Schaeffer and Collins[28] has shown that while these results are qualitatively correct for cis-2-phenylcyclohexanol, the trans isomer undergoes extensive rearrangement in phosphoric acid in addition to dehydration. The olefins resulting from trans-2-phenylcyclohexanol were identified as 1-phenylcyclohexene, 3-phenylcyclohexene, 4-phenylcyclohexene, 1-benzylcyclopentene and benzalcyclopentane occurring in varying amounts. 3-Phenylcyclohexene, the expected product, surprisingly constituted only 9% of the total material. We have carried out a cursory examination of the same reaction on cis- and trans-2-phenylcycloheptanol and find by ultraviolet analysis, as previously described, that the cis alcohol apparently gives ca. 50% 1-phenylcycloheptene, and the trans alcohol gives ca. 25% of the conjugated olefin. These results were confirmed by vapor phase chromatography. However, belying the validity of these measurements is the observation that 3-phenylcycloheptene is not stable under the reaction conditions. The olefin mixture resulting from the dehydration of trans-2-phenylcycloheptanol with phosphorus oxychloride was subjected to the action of phosphoric acid similar to the manner in which the dehydrations were carried out. Ultraviolet examination of the olefin mixture after this treatment showed a very strong maximum at 247 mμ corresponding to ca. 25% 1-phenylcycloheptene.

Before the treatment with phosphoric acid there was very little conjugated olefin present (see Table 3). A number of runs were remarkably reproducible as indicated by ultraviolet spectroscopy, but regardless of this the results are not useful for any but the most qualitative

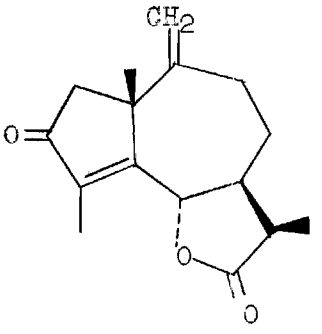
conclusions. It can be said, however, that in the absence of any appreciable decomposition of 1-phenylcycloheptene these percentages represent the upper limit of amount of the conjugated olefin formed. It is interesting to note above that 3-phenylcycloheptene does, assuredly, undergo extensive isomerization in 85% phosphoric acid, whereas 3-phenylcyclohexene is reported not to do so. The studies of Schaeffer and Collins[28] also indicate that the unreactivity of 3-phenylcyclohexene is questionable. An indication that cis- and trans-2-phenylcycloheptanol might display behavior analogous to that described by Schaeffer and Collins[28] is revealed by vapor phase chromatographic analyses of the dehydration products. Both of the alcohols yielded considerable material other than 1- and 3-phenylcycloheptene. The investigation of these other products was not undertaken.

It is interesting, in the light of current evidence, to examine recent work on the stereochemistry of a compound derivable from santonin by a unique light catalyzed rearrangement.[73] This compound, isophotosantonic lactone (XL) contains a bicyclo [3.5.0]-decane system in which the stereochemistry postulated is as indicated by structure XL. It has been proposed[74] that the opposite configuration prevailed at C-10, i.e., the hydroxyl and hydrogen at C-1 were trans and occupied quasi-axial positions. Dehydration studies[73] on isophotosantonic lactone afforded the fact that thionyl chloride in pyridine yielded an olefin (XLI) which resulted from the elimination of the hydroxyl and a hydrogen from the C-10 methyl group. On the assumption that there should be no difference in phosphorus oxychloride and thionyl chloride (both in pyridine) dehydrations as far as the end result is concerned, the now proven preference

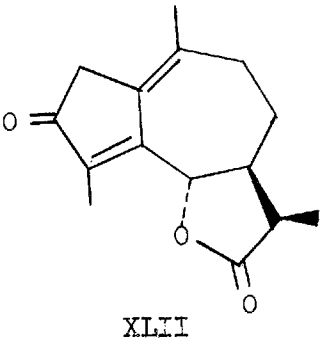
of phosphorus oxychloride for trans elimination in the cycloheptane series firmly establishes the stereochemistry at C-10[75] as being that represented in XL. In this structure the geometry of the dehydration is only satisfied by the C-10 methyl hydrogens and by neither the C-1 nor C-9 hydrogens. The possibility that some peculiarity of the ring system might preclude the formation of the conjugated olefin is eliminated by the fact that acid-catalyzed dehydrations[73] afford XLII.



XL

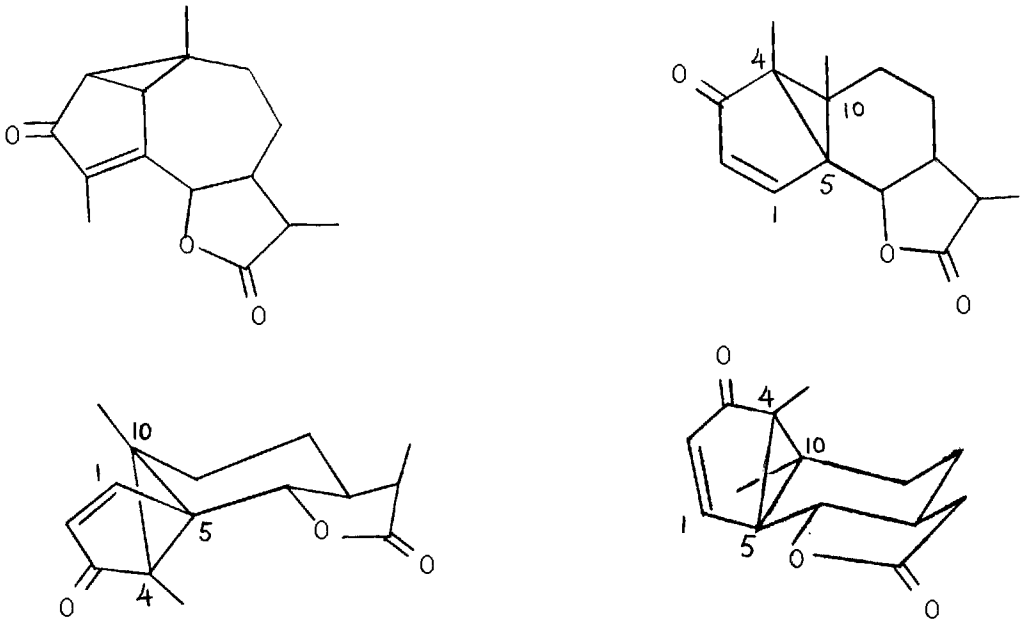


XLI



XLII

Considering this structure for isophotosantonic lactone (XL) the stereochemistry of the reaction producing this product should be reviewed. An intermediate (lumisantonin) in the formation of XL has been isolated after controlled irradiation of santonin and structures XLIII[76] and XLIV[77,78] have been proposed for this compound. The evidence for the gross structure XLIV seems sufficient to exclude other possibilities. Lumisantonin (XLIV) is converted to isophotosantonic lactone by boiling acetic acid in the dark which indicates an ionic rather than a free radical reaction. A probable mechanism of the rearrangement consists of the initial addition of a proton to the ketone oxygen of XLIV resulting in the formation of a non-classical carbonium ion involving C-1, C-4, C-5, and C-10. Attack of a nucleophilic



reagent, such as acetate ion completes the sequence. Barton and Gilham[77] have apparently established XLVI as the configuration of lumisantonin excluding a similar reasonable structure (XLV)[78] essentially on the basis of optical rotatory dispersion comparisons. It is difficult however, to rationalize the formation of isophotosantonic lactone with the stereochemistry as in XL from lumisantonin of the configuration XLVI. It seems that any reasonable mechanism for the hydration of lumisantonin to isophotosantonic lactone must be fairly concerted movement of electrons in order to avoid the formation of isomeric products, and it is difficult to see how a concerted sequence as described above can produce in a precedented manner the assigned structure for isophotosantonic lactone, XL.

It would seem that a re-investigation of the total stereochemical assignments in isophotosantonic lactone and lumisantonin is in order.

V. EXPERIMENTAL

trans-2-Phenylcycloheptanol.--(a) *trans*-2-Phenylcycloheptanol was prepared according to the method whereby Cook, Hewett, and Lawrence[50] prepared *trans*-2-phenylcyclohexanol. Phenyllithium was prepared by the addition of small pieces of freshly cut lithium to a solution of bromobenzene in ether maintained at ice bath temperature. The reaction mixture was stirred for *ca.* 1 hr.; approximately two-thirds of the lithium had dissolved. To the cold solution of phenyllithium an ether solution of cycloheptene oxide (a quantity equivalent to the theoretical amount of phenyllithium present) was added dropwise with stirring. The reaction mixture was maintained at ice bath temperature for *ca.* 30 min. and then boiled under reflux for *ca.* 2 hrs.; excess aqueous ammonium chloride was added, and the organic material isolated by extraction with ether. The ether extract was washed with sodium bicarbonate, dried, and concentrated on a steam bath at reduced pressure. The resulting oil was distilled at 113 - 114°/0.5 mm. to yield 25% of *trans*-2-phenylcycloheptanol.

The *p*-nitrobenzoate ester was prepared by reaction of the alcohol in dry pyridine with *p*-nitrobenzoyl chloride. Crystallization from 95% ethanol afforded pale yellow crystals, m. p. 84.0 - 85.0°.

Anal. Calc'd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.62; H, 6.01; N, 4.24.

trans-2-Phenylcycloheptanol.--(b) Sodium hydroxide (2.6 g., 0.065 mole)

was added to a mixture of 3.87 g. (0.0114 mole) trans-2-phenylcycloheptyl p-nitrobenzoate, 45 ml. of dioxane, and 19 ml. of water. The p-nitrobenzoate ester was derived from the crude product of an extended reduction, vide infra, of 2-phenylcycloheptanone with lithium aluminum hydride. The mixture was boiled under reflux on a steam bath for 9 hrs. The dioxane was removed from the tomato-red mixture at reduced pressure on a steam bath as the dioxane-water azeotrope; 100 ml. of water was added, and the mixture was extracted with three portions of chloroform. The extract was washed twice with water, dried, and the chloroform removed on a steam bath at reduced pressure yielding 2.04 g., 94%, of colorless oil. Short path distillation afforded 1.448 g., 67%, of trans-2-phenylcycloheptanol, n_D^{25} 1.5415.

Vapor phase chromatography of the distilled trans alcohol showed it to be homogeneous.

trans-2-Phenylcycloheptanol.--(c) A solution of 805 mg. (2.34 mmoles) of cis-2-phenylcycloheptyl p-toluenesulfonate in 4 ml. of dry benzene was applied to a column (2 x 20 cm.) of 67.5 g. of basic alumina† prepared in dry benzene. After standing at room temperature for 59 hrs. elution with 300 ml. of dry benzene afforded 256.6 mg., 64%, of olefinic material. Further elution with 300 ml. of 5% methanol in ether yielded 104.3 mg., 23.5%, of trans-2-phenylcycloheptanol.

The p-nitrobenzoate ester was prepared, m. p. 83.0 - 84.4°, mixed melting point with authentic trans-2-phenylcycloheptyl p-nitrobenzoate,

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†One pound of Merck acid-washed alumina was mixed with a solution of 50 g. of potassium hydroxide in 37 ml. of water. The powdery mixture was homogenized in a ball mill for 24 hrs. and dried at 220° for 3-4 days.[63]

83.3 - 84.6°.

trans-2-Phenylcycloheptyl p-Toluenesulfonate.--trans-2-Phenylcycloheptanol (1.106 g., 0.006 mole) was dissolved in 20 ml. of dry pyridine, cooled in ice, and 1.520 g. (0.008 mole) of p-toluenesulfonyl chloride was added in one portion. The mixture was allowed to stand in a melting ice bath and then at room temperature for three days. Excess saturated sodium bicarbonate solution and water were added. The precipitated trans-2-phenylcycloheptyl p-toluenesulfonate was collected, washed well with water, and air dried yielding 1.23 g., m. p. 96.0 - 96.4°. The melt was heterogeneous at the melting point. The aqueous portion of the reaction mixture was extracted several times with chloroform, which was washed with hydrochloric acid, dried, and concentrated at reduced pressure yielding solid material. Crystallization from cyclohexane gave 0.15 g. of white crystals. This portion was combined with that obtained directly giving a total yield of 1.38 g., 69%. Crystallization from cyclohexane afforded 1.003 g., 50%, of trans-2-phenylcycloheptyl p-toluenesulfonate, m. p. 82 - 83° dec. (heterogeneous at the melting point).

Drying of a portion at 80° for 14 hrs. at oil pump pressure caused extensive decomposition to occur resulting in a brown gum with only a 2.5% loss in weight. The gum, extracted exhaustively with cyclohexane, yielded a glass. Subsequent extraction with hot chloroform and concentration of the extracts afforded a crystalline, hygroscopic substance in ca. 10% yield by weight, m. p. 91 - 100°. p-Toluenesulfonic acid is reported to melt at 106°.[79]

Reduction of 2-Phenylcycloheptanone - Short Reaction Time.--A slurry of 12.2 g. (0.32 mole) of lithium aluminum hydride in 375 ml. of dry ether was prepared and stirred for ca. 5 min. The flask was cooled in an ice bath, and a solution of 30 g. (0.16 mole) of 2-phenylcycloheptanone in 200 ml. of dry ether was added dropwise over a period of 15 min. The reaction was maintained at ice bath temperature and stirred for 70 min. One hundred milliliters of ethyl acetate was added dropwise, followed by 60 ml. of water and 250 ml. of 6N hydrochloric acid. The layers were separated and the aqueous phase washed two times with ether; the ether portions were combined, washed once with dilute sodium bicarbonate, dried, and the ether removed under reduced pressure on a steam bath. Remaining ethyl acetate was removed with a stream of dry air yielding ca. 30 g. of oil. See Table 2 for analysis of the product mixture.

A 6.6 g. (0.035 mole if all were alcohol) portion of the crude product was dissolved in 25 ml. of dry pyridine, cooled in ice, and 12.0 g. (0.061 mole) of p-toluenesulfonyl chloride was added in one portion. The mixture was swirled for a few minutes, allowed to stand in a melting ice bath and then at room temperature for three days. Excess saturated sodium bicarbonate solution was added with cooling, and the mixture extracted with several portions of chloroform. The chloroform was washed well with dilute hydrochloric acid, dried, and removed (below 50°) at reduced pressure to yield 8.006 g. of oil which did not solidify upon refrigeration overnight. The oil was dissolved in 150 ml. of low-boiling petroleum ether, and the crystals which formed after several hours of refrigeration were collected and washed with petroleum ether, yield 1.402 g., 12%, m. p. 81.5 - 106°. The melt became heterogeneous suddenly at 117°. Recrystal-

lization four times from cyclohexane not exceeding 60° yielded 132.3 mg., 1.1% (if all starting material were alcohol) of trans-2-phenylcycloheptyl p-toluenesulfonate, m. p. 83.5 - 84.0° dec. The melt was heterogeneous at the melting point.

Anal. Calc'd. for $C_{20}H_{24}O_3S \cdot 2H_2O$: C, 63.13; H, 7.42. Found: C, 63.92; H, 6.82. The analytical sample was dried in an Abderhalden drying apparatus overnight at room temperature.

Another portion of the crude product (5.0 g., 0.026 mole if all were alcohol) was dissolved in 20 ml. of dry pyridine and treated with 9.25 g. (0.05 mole) of p-nitrobenzoyl chloride at room temperature. The mixture was allowed to stand without cocling for 1 hr. Water was added, and the mixture extracted with chloroform. Washing of the chloroform extract with sodium bicarbonate and dilute hydrochloric acid, drying, and removal of the solvent gave an oil. The oil was taken up in 200 ml. of 95% ethanol, filtered, and concentrated to 50 ml. on a steam bath. After refrigeration the solid was collected and air dried yielding 2.566 g., m. p. 81.0 - 88.0°. Eight crystallizations from hot 95% ethanol afforded 0.996 g., 11%, of cis-2-phenylcycloheptyl p-nitrobenzoate, m. p. 92.0 - 93.2°.

Anal. Calc'd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 71.00; H, 6.08; N, 4.16.

Reduction of 2-Phenylcycloheptanone - Extended Reaction Time.--A solution of 25.0 g. (0.133 mole) of 2-phenylcycloheptanone in 100 ml. of dry ether was added during 1 hr. with stirring to 9.9 g. (0.26 mole) of lithium aluminum hydride in 500 ml. of dry ether. The reaction mixture was kept

cold for 1.5 hrs., boiled under reflux for 9 hrs., and stirred at room temperature overnight. Seventy milliliters of ethyl acetate was added followed by 100 ml. of water and 200 ml. of 6N hydrochloric acid. The layers were separated, and the aqueous phase extracted with two portions of ether. The combined ether extracts were washed with sodium bicarbonate solution, dried, and concentrated on a steam bath at reduced pressure, yielding 24.3 g., 96%.

Preparation of the p-nitrobenzoate ester with p-nitrobenzoyl chloride in pyridine afforded an oil which was crystallized from 95% ethanol giving a 67% yield, m. p. 78 - 87°. Two more crystallizations afforded impure material, m. p. 82.5 - 90.0°.

Reduction of 2-Phenylcycloheptanone with Lithium Aluminum Hydride - Aluminum Chloride.--[61] To 400 ml. of dry ether cooled in an ice bath was added slowly, with stirring, 53.4 g. (0.400 mole) of aluminum chloride followed by 3.79 g. (0.100 mole) of lithium aluminum hydride. This mixture was allowed to stir at ice bath temperature for 1 hr., at which time 38.25 g. (0.203 mole) of 2-phenylcycloheptanone dissolved in 100 ml. of dry ether was added during 25 min. The ice bath was removed and the mixture was boiled under reflux with continued stirring for 12 hrs. Forty-five milliliters of water was added followed by 300 ml. of 10% sulfuric acid; the layers were separated, and the aqueous phase was extracted with two portions of ether. The ethereal extract was washed with one portion of 5% sodium bicarbonate, dried, and concentrated on a steam bath at reduced pressure yielding 38.1 g. of crude product. See Table 1 for analysis of the product mixture.

cis-2-Phenylcycloheptanol.--(a) trans-2-Phenylcycloheptyl p-toluenesulfonate (1.506 g., 4.38 mmoles) dissolved in 8.0 ml. of dry benzene was applied to a column of basic alumina, vide supra, (127 g., 4.5 x 18 cm.) prepared in dry benzene, and washed on with eight 1 ml. portions of dry benzene. The column was allowed to stand at room temperature for 61 hrs. Elution with 300 ml. of benzene gave 373.5 mg., 50%, of colorless oil. The next 400 ml. of benzene eluate was discarded as was the initial 100 ml. of methanol-ether. Further elution with 200 ml. of 5% methanol in ether gave 332.1 mg., 40%, of cis-2-phenylcycloheptanol as a colorless oil.

The p-nitrobenzoate was prepared in the usual way, m. p. 91.5 - 93.5°, mixed melting point with authentic cis-2-phenylcycloheptyl p-nitrobenzoate, 91.8 - 93.2°.

cis-2-Phenylcycloheptanol.--(b) The saponification of cis-2-phenylcycloheptyl p-nitrobenzoate derived from a short reduction, vide supra, of 2-phenylcycloheptanone with lithium aluminum hydride was carried out in the same way as for trans-2-phenylcycloheptyl p-nitrobenzoate. cis-2-Phenylcycloheptanol was obtained after saponification as a colorless oil; distillation afforded a fraction boiling at 98.5 - 102.5°/0.25 mm., yield 72%, n_D^{25} 1.5436.

cis-2-Phenylcycloheptyl p-Toluenesulfonate.--To a cold solution of 1.66 g. (8.73 mmoles) of cis-2-phenylcycloheptanol in 8 ml. of dry pyridine was added 2.49 g. (13.10 mmoles) of p-toluenesulfonyl chloride. The mixture was allowed to stand in a melting ice bath and then at room temperature

for 3 days. The flask was chilled in ice and excess sodium bicarbonate solution was added. The mixture was extracted with chloroform and the extract washed with dilute hydrochloric acid, dried, and concentrated below 50°, under reduced pressure, to yield 2.402 g., 80%, of cis-2-phenylcycloheptyl p-toluenesulfonate as an oil which crystallized fully on standing ca. 2 hrs. at room temperature. The white solid was crystallized three times from cyclohexane, maintained below 60°, to yield 830 mg., 28%, of small white crystals, m. p. 91.7 - 93.0°. The melt became heterogeneous at 104°.

Anal. Calc'd. for $C_{20}H_{24}O_3S \cdot 2H_2O$: C, 63.13; H, 7.42. Found: C, 63.64; H, 6.91. The analytical sample was dried in an Abderhalden drying apparatus overnight at room temperature.

Phenylcycloheptane.--A mixture of cis- and trans-2-phenylcycloheptyl p-toluenesulfonates (3.49 g., 0.0101 mole) in the minimum amount of dry ether to effect solution (ca. 200 ml.) was added to a slurry of 0.38 g. (0.01 mole) of lithium aluminum hydride in 30 ml. of dry ether at room temperature.[80] After boiling under reflux for 20 hrs. an additional 0.3 g. (0.008 mole) of lithium aluminum hydride was added, and boiling continued for another 21 hrs. One hundred milliliters of water was added slowly with ice bath cooling followed by 100 ml. of 6N hydrochloric acid. The layers were separated; the aqueous phase was extracted with one portion of ether, and the combined ethereal extracts were washed with one portion of sodium bicarbonate, dried, and concentrated on a steam bath, yielding 1.727 g., 98%, of crude phenylcycloheptane.

The crude product was chromatographed on 150 g. (3.2 x 17.0 cm.)

of acid washed alumina prepared in and eluted with low-boiling petroleum ether. The first 150 ml. of eluate containing 80.9 mg. was discarded. The next 100 ml. of eluate was collected and evaporated to yield 1.330 g., 76%, of colorless oil. Further elution with 150 ml. of petroleum ether produced 134.9 mg. of residue. The middle fraction was distilled through a short path apparatus to yield 0.728 g., 41%, of phenylcycloheptane, n_D^{25} 1.5254. The reported value is n_D^{25} 1.5287.[81] Vapor phase chromatography showed the product to be homogeneous.

1-Phenylcycloheptene.--Phenylmagnesium bromide, prepared from 14.9 g. (0.095 mole) of bromobenzene in 75 ml. of dry ether was treated with 10.0 g. (0.089 mole) of cycloheptanone according to Baddeley, Chadwick, and Taylor[72] in the usual Grignard fashion. Completion of the reaction yielded crude 1-phenylcycloheptanol. Dehydration and fractional distillation afforded 7.04 g., 46%, of 1-phenylcycloheptene, b. p. 74.5 - 76.5/0.3 mm., n_D^{25} 1.5575, λmax., 247 mμ, ϵ, 14,000. The reported boiling point is 113 - 115°/8 mm. and n_D^{20} 1.5624.[82] The λmax. reported is 247 mμ (ϵ = 11,500).[72] Vapor phase chromatography showed the product to be homogeneous.

2-Phenylcycloheptanone.--(a) 2-Phenylcycloheptanone was prepared from benzylamine, ethyl chloroformate, and cyclohexanone according to Organic Syntheses.[55] The crude product was fractionated at 0.3 mm., and the portion boiling at 100 - 113° was collected, yield 46%, n_D^{28} 1.5389.

Upon addition of 2,4-dinitrophenylhydrazine reagent[83] to the ketone in ethanol a red precipitate formed in addition to the yellow-orange

derivative. Crystallization from 95% ethanol did not remove the red material, but ethanol-ethyl acetate did afford only the yellow-orange 2,4-dinitrophenylhydrazone, m. p. 169 - 172°. Melting points reported for this derivative are 170° dec.[53] and 171 - 172°.[54]

Vapor phase chromatography showed the 2-phenylcycloheptanone to be homogeneous.

2-Phenylcycloheptanone.--(b) Kiliani's reagent, prepared according to Sato and Ikekawa,[52] was added dropwise to 244 mg. (1.28 mmoles) of trans-2-phenylcycloheptanol in 2 ml. of redistilled acetone until a greenish-orange color was permanent (ca. 0.7 ml.). During the addition a very dark oil separated and settled. Water was added and then 5% sodium hydroxide until the mixture was alkaline. Extraction with chloroform and removal of the solvent gave a yellow oil which was taken up in 95% ethanol and treated with 2,4-dinitrophenylhydrazine reagent.[83] The yellow precipitate was collected, washed with 95% ethanol, and dissolved in ca. 6 ml. of ethyl acetate which was filtered and evaporated to 0.5 ml. One-half milliliter of 95% ethanol was added, whereupon crystallization occurred immediately. The flask was cooled, and the 2-phenylcycloheptanone 2,4-dinitrophenylhydrazone collected, m. p. 168.5 - 171.5°. A mixed melting point with the same derivative of authentic 2-phenylcycloheptanone showed no depression, i.e., 170.0 - 173.0°.

2-Phenylcycloheptanone.--(c) cis-2-Phenylcycloheptanol (268.5 mg., 1.41 mmoles) was dissolved in 2 ml. of redistilled acetone. Kiliani's reagent[52] was added dropwise until a greenish-orange color was permanent (ca. 1 ml.).

Water (25 ml.) and 5% sodium hydroxide (25 ml.) were added and the mixture extracted with four 10 ml. portions of chloroform. The extract was dried and the solvent removed under reduced pressure yielding 211 mg., 79%, of 2-phenylcycloheptanone.

The 2,4-dinitrophenylhydrazone was prepared, m. p. 170.8 - 171.3°, mixed melting point with authentic 2-phenylcycloheptanone 2,4-dinitrophenylhydrazone, 171.0 - 172.5°.

Dehydration of cis-2-Phenylcycloheptanol with Phosphorus Oxychloride in Pyridine.--[84] cis-2-Phenylcycloheptanol (121.8 mg., 0.642 mmole) was dissolved in 2.0 ml. of dry pyridine. Phosphorus oxychloride (0.15 ml.) was added slowly, and the solution, protected with a calcium chloride tube, was warmed on a steam bath for 1 hr. The clear, colorless solution was cooled, diluted with 3 ml. of water, and extracted with four 1 ml. portions of ether. The extract was washed with three 1 ml. portions of 6N hydrochloric acid, dried, and the ether was removed under a stream of dry nitrogen, yielding 102.7 mg., 93%, of clear, virtually colorless oil.†

Dehydration of trans-2-Phenylcycloheptanol with Phosphorus Oxychloride in Pyridine.--The same procedure was followed as for cis-2-phenylcycloheptanol yielding 89% of a clear, colorless oil.†

Dehydration of cis-2-Phenylcycloheptanol with Phosphoric Acid.--A mixture of 121.4 mg. (0.640 mmole) of cis-2-phenylcycloheptanol and 206.6 mg.

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†See Tables 2 and 3 for analyses of the dehydration mixtures.

of 85% phosphoric acid was maintained at 150 - 200° for 3 hrs. The mixture was cooled, diluted with 2 ml. of water, and extracted with four 2 ml. portions of ether. The ether extract was washed with two 2 ml. portions of 5% sodium hydroxide, dried, and concentrated under a stream of dry air to yield 101.2 mg., 92%, of yellow oil.

Dehydration of trans-2-Phenylcycloheptanol with Phosphoric Acid.--The same procedure was followed as for cis-2-phenylcycloheptanol, yielding 84% of yellow oil.

Treatment of 3-Phenylcycloheptene with Phosphoric Acid.--The crude product, 38.3 mg., obtained from the dehydration of trans-2-phenylcycloheptanol with phosphorus oxychloride was heated with 76.7 mg. of 85% phosphoric acid in a manner similar to the phosphoric acid dehydrations. Isolation of the ether soluble fraction provided 30.2 mg. of brown oil. Quantitative ultraviolet spectroscopic measurements using the extinction at 247 mμ ($\lambda_{max.}$) showed that the product contained ca. 25% 1-phenylcycloheptene.

Gas Chromatographic Analyses.--Before analysis the pure substances and the reduction mixtures were flash distilled through a short path apparatus in addition to other treatment stated. The dehydration mixtures in solution with dry benzene were filtered through a short column of acid-washed alumina. The gas chromatographic analyses† were conducted on a 6 ft. x 4 mm.

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†The author is very grateful to Dr. Charles C. Sweeley of the University of Pittsburgh who so generously consented to do the gas chromatographic analyses.

glass column packed with General Electric silicone gum (SE 30) coated on 80 - 100 mesh Chromosorb W (ca. 3% silicone by wt.). The column was maintained at 153° with an inlet pressure of 16.5 psi. of argon. The flow rate of gas under these conditions was ca. 30 ml./min.

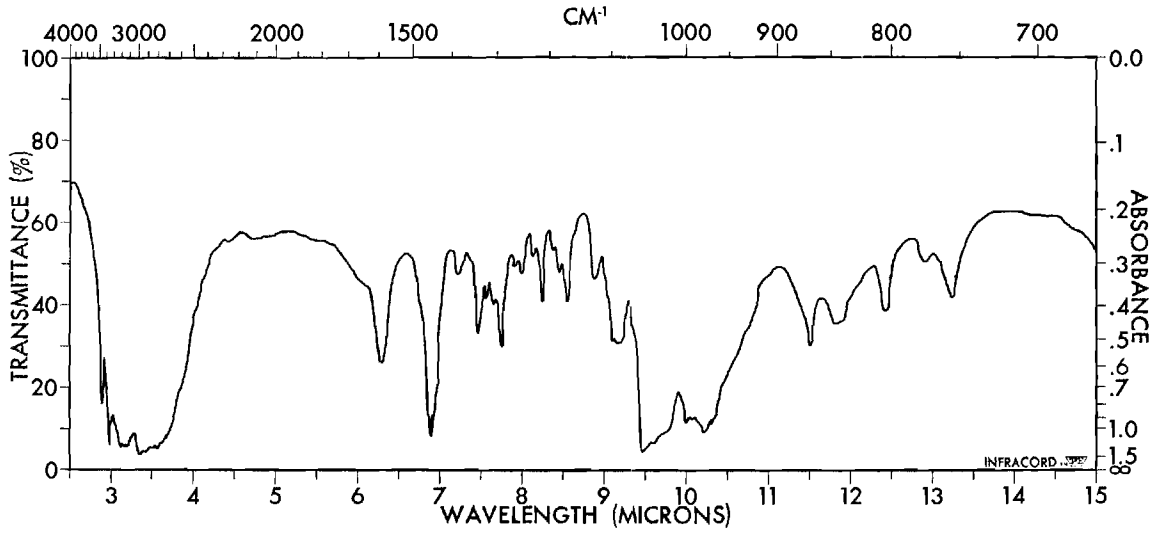

Figure 3. Infrared Spectrum of trans-2-Aminocycloheptanol.

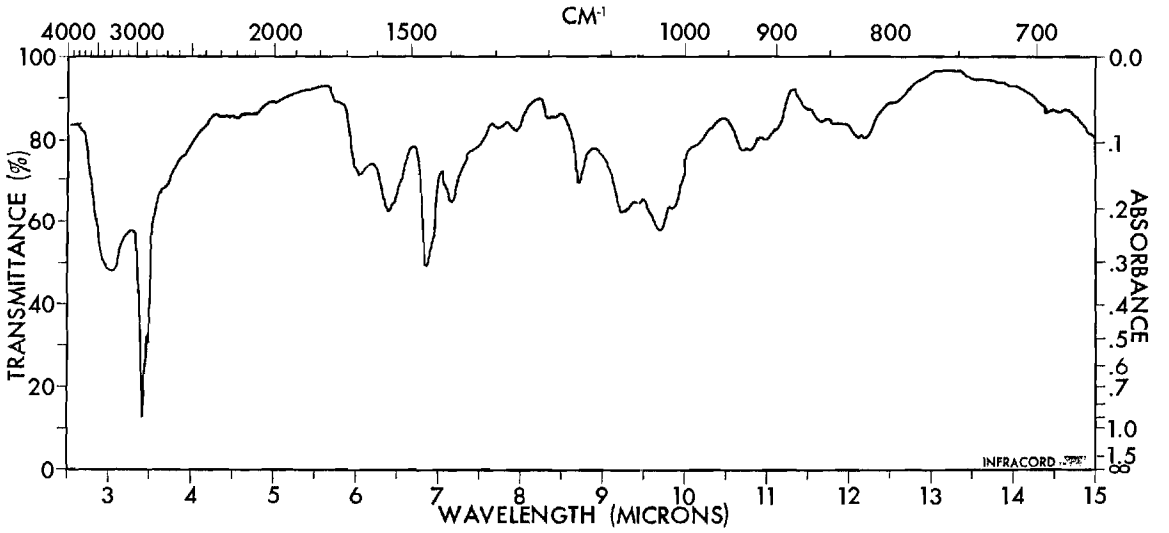

Figure 4. Infrared Spectrum of cis-2-Aminocycloheptanol.

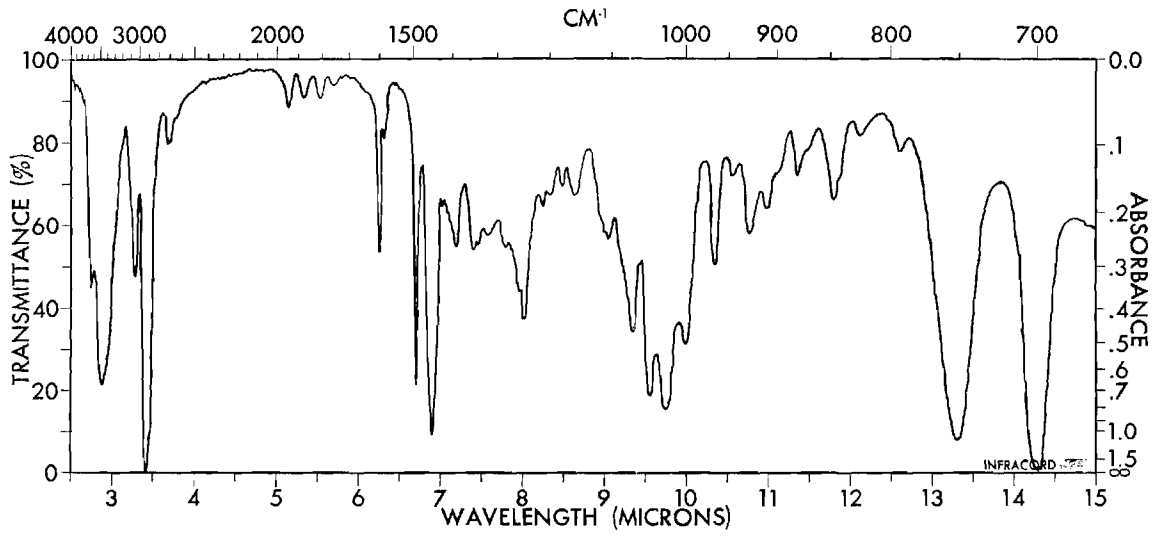

Figure 5. Infrared Spectrum of trans-2-Phenylcycloheptanol.

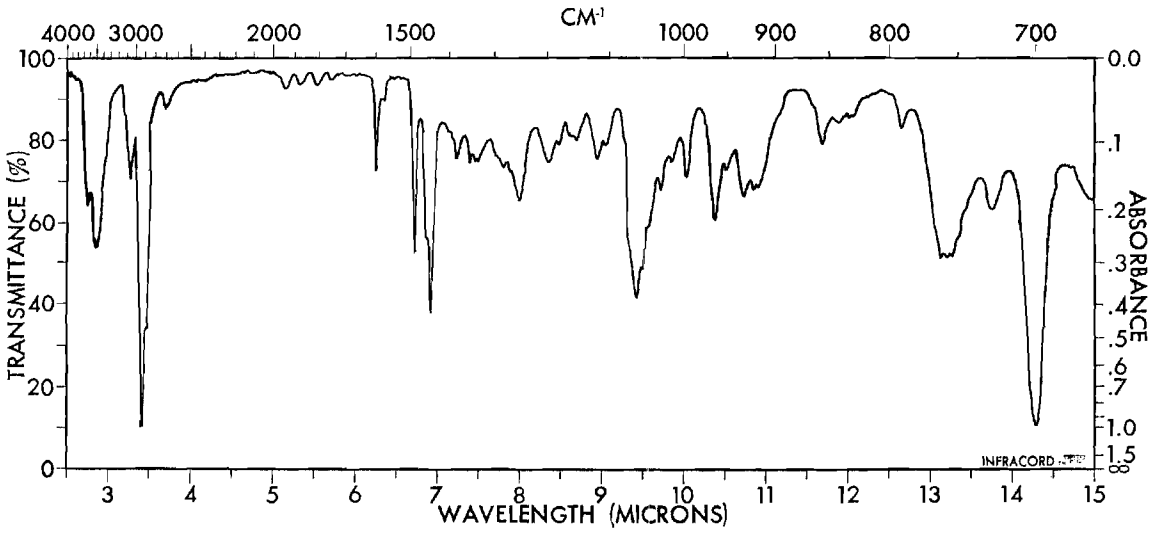

Figure 6. Infrared Spectrum of cis-2-Phenylcycloheptanol.

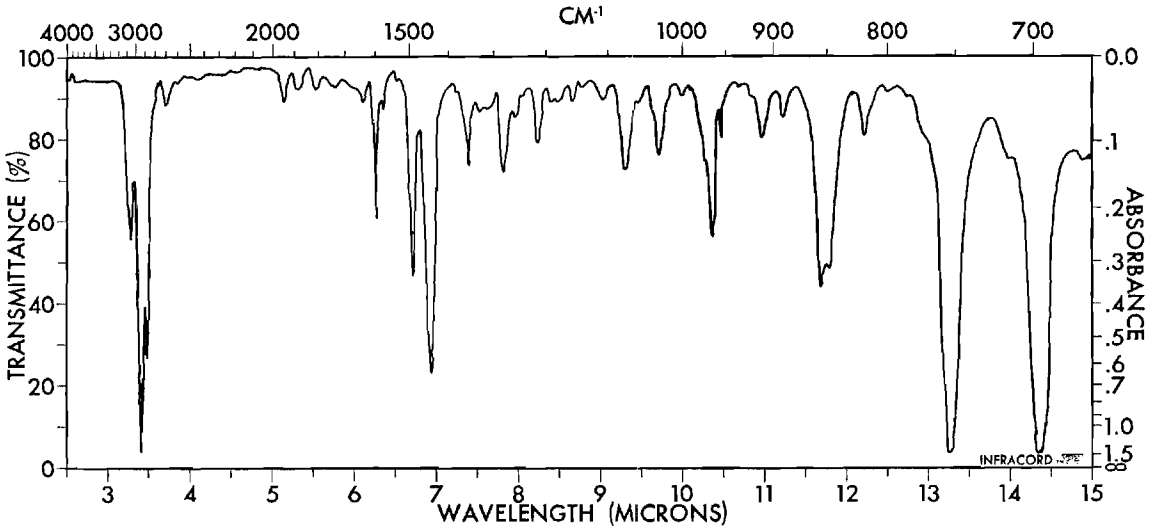

Figure 7. Infrared Spectrum of 1-Phenylcycloheptene.

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